Inhaler Resistance, Flowrate and Duration of Inhalation: The Effort to Use an Inhaler Adequately.

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Summary

As chronic obstructive pulmonary disease (COPD) becomes more severe, the ability of the patient to perform the correct inhalation manoeuvre becomes progressively limited and may fall below that required for correct use. The physiological effort associated with achieving this has seldom been expressed with the focus on peak inspiratory flow and resistance: duration and flow profile are also important. We have quantified the effort of untrained and trained moderate (n=12) and very severe (n=10) COPD volunteers to use seven commonly used pMDI, DPI and SMI devices in a minimally adequate way (n=6: Evohaler®, Respimat®, HandiHaler®, Breezhaler®, Turbohaler®, Ellipta®, and NEXThaler®). Patient flow profiles, at three resistances (0.04, 0.16 and 1.00 $kPa^{½}/L.min^{-1}$) were accessed from a database, enabling interpolation and modelling to the devices. Device resistances were measured and enumerated at the device-effective flowrate. Duration of inhalation was determined from the literature, combined with an assessment of time for actuation/coordination, aerosol delivery, 'chase' air, and capsule emptying. Energy (airWatts, aW), was calculated as volume ($m^3.sec^{-1}$) x pressure (kPa). To provide a comparable value for each inhaler, Energy (aW) was multiplied by duration (sec) to express the Effort of inhalation. The data show that training helps subjects to exert a greater effort. Untrained subjects who produced insufficient Effort or who were close to failure were able to deliver adequate Effort following training. Devices that propel the medication towards the patient (pMDI, SMI) require less inspiratory Effort. Post-training, all of the devices were within the theoretical capability of the subjects for successful use.

Key Message

A new patient-inhaler parameter (inspiratory Effort) has shown that untrained subjects exert less effort than trained subjects, and that some inhalers require an inspiratory effort that is beyond the capability of the untrained subject: for those devices training must be regarded as a necessity.

Introduction

Patients taking inhaled medication need to be able to use their inhaler correctly to ensure effective treatment. Many patients believe that they are doing so when, in reality, they are making important errors [1]. Correct inhaler use entails not only preparing the device but also making an inspiratory manoeuvre appropriate to receive the medication: the slow gentle deep inhalation for pressurised metered dose inhalers (pMDIs) and the fast, powerful, deep inhalation for dry powder inhalers (DPIs) [1]. Much has been written about the difficulties patients have with technique and particularly with the appropriate inspiratory flowrate [2]. As chronic obstructive pulmonary disease (COPD) and asthma—the latter particularly during periods of worsening control—become more severe, the ability of the patient to perform the correct inhalation manoeuvre becomes progressively limited and may fall below the level required for the correct use of a particular inhaler [2-3]. The physiological effort associated with achieving this has seldom been expressed. Previously studies have focused largely on peak inspiratory flowrate and resistance, ignoring the impact of duration or the full importance of the flow profile [4-6].

We have sought to quantify the patient effort required to use particular devices in a minimally adequate way, using the three elements that contribute to that effort: (i) the resistance of the inhaler to air flow, (ii) the inhalation flowrate necessary for acceptable use, and (iii) the duration of inhalation. By considering duration as well as flowrate and resistance we can express inhalation as an effort. We investigated the inspiratory effort that subjects with COPD could apply relative to the effort necessary for minimally successful inhaler use. We have completed these effort determinations for seven commonly used inhaler devices.

Experimental methods

Firstly, we accessed a database of inspiratory profiles for COPD subjects classified by severity (moderate: FEV_1 50%-80% predicted, severe: 30%-50% and very severe <30%) [7]. The subjects had been asked to inhale (without training) through three different resistances (0.04, 0.16 and 1.00 $kPa^{½}/L.min^{-1}$). They were then trained to inhale forcefully, and asked again to inhale against the three resistances. These flow profile data enable interpolation and modelling to a range of different device resistances that cover marketed inhaler products.

Secondly, we obtained six replicates of seven commercial inhaler devices (Table 1) and measured device resistance for each device using the Clark and Hollingworth method [8]. All measurements were made on the same calibrated equipment, by the same operator (AG) and in the same laboratory. The devices were a pMDI (Evohaler®, GSK), a Soft Mist™ inhaler (SMI, Respimat®, Boehringer Ingelheim), high resistance and low resistance capsule DPIs (HandiHaler®, Boehringer Ingelheim and Breezhaler®, Novartis), high resistance reservoir and low resistance blister DPIs (Turbohaler®, AstraZeneca and Ellipta®, GSK) and a breath actuated reservoir DPI (NEXThaler®, Chiesi). Active pharmaceutical ingredients are provided in the footnote. The mean resistance for each device was interpolated at the flowrate considered effective for that device as determined from the literature [9-12].

Device	Type	Image	Flow ($L.min^{-1}$)	Flow (volume) ($m^3.sec^{-1}$)	Duration (seconds)	Resistance ($kPa^{1/2}/L.min^{-1}$)	Batch No.	Expiry
Evohaler	pMDI		10	0.00017	2.50	0.01	EL5H	05-2019
Respimat	SMI		20	0.00033	2.50	0.03	701452A	02-2020
HandiHaler	c-DPI		20	0.00033	2.50	0.14	702818	03-2019
Breezhaler	c-DPI		50	0.00083	1.50	0.05	BV164	12-2018
Ellipta	b-DPI		30	0.00050	2.00	0.07	R825657	06-2019
Turbohaler	r-DPI		30	0.00050	2.00	0.10	XFSB	08-2019
NEXThaler	r-DPI		35	0.00058	1.75	0.11	1062477	07-2020

Table 1 – Details and properties of the Inhaler devices (c = capsule, b = blister, r = reservoir)

We then attributed values to each device for a minimum effective inspiratory flowrate based on manufacturers' information and supported by studies at a range of different flowrates [9-10]. Similarly, published references were used where available for the duration of inhalation to achieve minimally correct usage [13], combined with a pragmatic assessment of the total timing for actuation/coordination, delivery of aerosol and the 'chase' air that drives the drug into the lung [9]. In the case of the capsule devices (Breezhaler and HandiHaler), we also conducted confirmatory testing by connection to a precision vacuum pump (Copley LCP5, Copley Scientific Limited, Nottingham, UK) to ensure that capsule rattle—the signal of capsule movement and thereby powder displacement—and capsule emptying were within pre-determined times at a particular flowrate. In the case of devices that are manually actuated (pMDI, Respimat) a time factor for coordination was considered: based on earlier work with Respimat we adopted a 0.5s coordination time [13].

The components of an inspiratory effort determination per device were therefore available. Inspiratory Effort (airWatts per inhalation, aW) was calculated as volume ($m^3.sec^{-1}$) x pressure (kPa) x duration (seconds). The modelling for moderate (n=12) and very severe (n=10) COPD patients both untrained and trained are presented.

Results

Flowrate, resistance, and duration data are given in Table 1. Ideal inspiratory Effort values (airWatts per inhalation), and those for untrained and trained COPD subjects are given in Table 2. Within inhaler, the untrained/ trained ideal values differ slightly owing to the zero to peak acceleration portion of the ideal profiles (which are based on the subject profiles). The ratio of ideal to subject ability to generate a minimally adequate Effort is given as a percentage: failure being represented by >100%. An example of an inspiratory flow profile in untrained and trained subjects (mean values) is given in Figure 1.

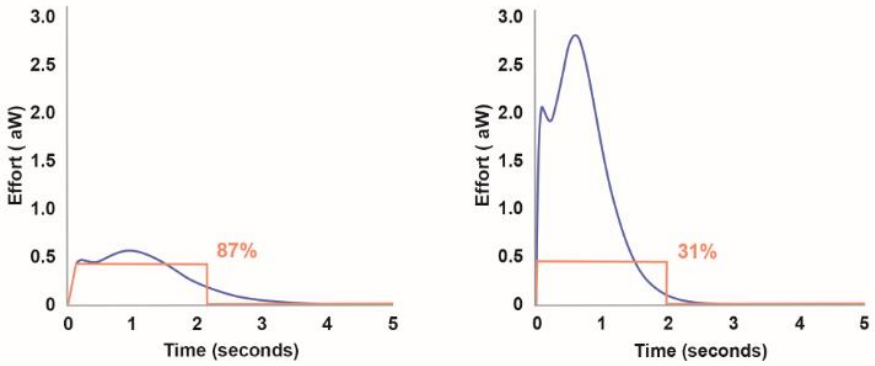

Figure 1 – Turbohaler: modelled flow profiles in untrained (left) and trained (right) very severe COPD subjects (mean, n=10). subject Effort; ideal Effort.

Device	Type	Moderate COPD (FEV_1 50-80% predicted)					
		UNTRAINED			TRAINED		
		Ideal	Subject (mean)	Effort %	Ideal	Subject (mean)	Effort%
Evohaler	pMDI	0.0006	0.15	0.4	0.0008	0.47	0.2
Respimat	SMI	0.03	0.76	3.9	0.05	2.20	2.3
HandiHaler	c-DPI	0.70	2.53	27.7	0.80	6.90	11.6
Breezhaler	c-DPI	0.87	1.58	55.1	1.00	4.10	24.4
Ellipta	b-DPI	0.40	1.68	23.8	0.40	4.10	9.8
Turbohaler	r-DPI	0.87	2.44	35.7	0.90	5.70	15.8
NEXThaler	r-DPI	1.80	3.15	57.1	1.50	7.50	20.0

Device	Type	Very Severe COPD (FEV_1 <30% predicted)					
		UNTRAINED			TRAINED		
		Ideal	Subject (mean)	Effort %	Ideal	Subject (mean)	Effort %
Evohaler	pMDI	0.0005	0.06	0.8	0.0003	0.15	0.2
Respimat	SMI	0.03	0.29	10.3	0.03	0.80	3.8
HandiHaler	c-DPI	0.67	1.62	41.4	0.80	3.60	22.2
Breezhaler	c-DPI	0.70	0.57	122.8	0.90	1.70	52.9
Ellipta	b-DPI	0.37	0.61	60.7	0.40	1.90	21.1
Turbohaler	r-DPI	0.89	1.02	87.3	0.90	2.90	31.0
NEXThaler	r-DPI	1.80	1.42	126.8	1.50	3.80	39.5

Table 2 - Inspiratory Effort values

Discussion

It is well recognised that the effort of using inhalers varies with their specific resistance but few studies have considered the influence of duration on the ability of the subject to generate the effort necessary to use a particular device. Inspiratory power and energy research in healthy paediatric and adult volunteer users of DPIs found age- and height-related effects and provided recommendations linking device resistance to comfort of use [14]. Determination of inspiratory manoeuvre duration is important and with a move to incorporate objective measures of inhaler performance this parameter will need to be properly mapped for future developments. Our work has been based on a pragmatic rationalisation that some chase air is needed to carry the medication deep into the lung and we attributed an approximate volume of one litre. For inhalers that deliver the dose very rapidly, the chase air duration follows delivery but for those with slower delivery the chase air begins during the delivery and extends, to some extent, post-delivery. We have attributed durations that are justified by pragmatic reasoning, but arguably different values could be rationalised.

Known 'optimal' flowrates and capsule emptying are not necessarily a marker of adequate delivery because higher flowrates may be necessary to drive powder deagglomeration [2]. For example we did note that the Breezhaler capsule emptied at 21 $L.min^{-1}$ but a minimum flowrate of 50 $L.min^{-1}$ is recommended from the literature [9]. The higher resistance of the HandiHaler brings more separation force to the powder at a lower flowrate and clinical studies have identified 20 $L.min^{-1}$ as adequate [9]. The implication of this is that a patient could achieve successful delivery from the HandiHaler at a rate at which Breezhaler would not work, and that to achieve successful minimally adequate delivery from Breezhaler the patient would be required to exert greater effort.

Unsurprisingly, the two devices that propel the medication towards the patient (pMDI, SMI) require markedly less inspiratory Effort than the DPIs studied. Not all medications are available via the pMDI and the SMI delivery systems. The necessity of multiple inhaler use for any chronic patient leads not to the conclusion that all patients should use low Effort requirement inhalers but that a clearer appreciation of the different inspiratory Effort requirements and appropriate training are necessary to ensure minimally adequate delivery. This is underpinned by the finding that—post-training—all of the devices were within the theoretical capability of the subjects for successful use.

The other immediate observation from the current data is that training helps subjects to exert a greater effort. The modelling indicates that subjects who could not produce sufficient Effort or who were close to failure when using a device in an untrained, spontaneous manner were then able to deliver adequate Effort following training. This appears most relevant to devices with a higher Effort requirement and in the very severe subjects; for example, Breezhaler, Turbohaler and NEXThaler.

In general, our results reveal that untrained subjects exert less effort than trained subjects and this supports the call for inhaler technique training that is made in most guidelines. Some inhalers require an inspiratory effort that is beyond the capability of the untrained subject, and for those devices training must be regarded as an absolute necessity. Interestingly, a recent study of the cost-effectiveness of improving suboptimal inhaler adherence (use and technique) in COPD patients calculated that intervention—including training—would result in worthwhile economic and clinical benefits [15].

Conclusion

The data indicate that COPD severity has an important influence on ability to use inhalers. Some inhalers may be beyond the capability of some COPD subjects to use correctly. While DPI inhalers appear similar in a higher Effort requirement, there are powder-presentation effects, *e.g.* duration of capsule emptying that may be clinically relevant. Inspiratory Effort assessments may represent an important consideration for inhaler device selection and merit further investigation.

Footnote

Evohaler pMDI (100μg salbutamol); **Respimat** SMI (2.5μg tiotropium / 2.5μg olodaterol); **HandiHaler** capsule DPI (18μg tiotropium); **Breezhaler** capsule DPI (85μg indacaterol / 43μg glycopyrronium); **Ellipta** blister DPI (55μg umeclidinium / 22μg vilanterol); **Turbohaler** reservoir DPI (160μg budesonide / 4.5μg formoterol); **NEXThaler** reservoir DPI (100μg beclomethasone / 6μg formoterol).

References

1 Price D, Bosnic-Anticevich S, Briggs A, Chrystyn H, Rand C, Scheuch G, Bousquet J: *Inhaler competence in asthma: Common errors, barriers to use and recommended solutions*, Respir Med 2013; 107: pp37-46. DOI: 10.1016/j.rmed.2012.09.017

2 Rau JL: *Practical problems with aerosol therapy in COPD*, Respir Care 2006; 51: pp158-172.

3 Al-Showair RAM, Tarsin WY, Assi KH, Pearson SB, Chrystyn H: *Can all patients with COPD use the correct inhalation flow with all inhalers and does training help?*, Respir Med 2007; 101: pp2395-2401. DOI: 10.1016/j.rmed.2007.06.008

4 Dunbar CA, Morgan B, Van Oort M, Hickey AJ: *A comparison of dry powder inhaler dose delivery characteristics using a power criterion*, PDA J Pharm Sci Tech 2000; 54: pp478-484.

5 Pohlmann G, Hohlfeld JM, Haidl P, Pankalia J, Cloes RM: *assessment of the power required for optimal use of current inhalation devices*, J Aerosol Med Pulmon Drug Del 2018; 31: pp1-8. DOI: 10.1089/jamp.2017.1376

6 Bischofberger J, Rhima CE, Tibbatts J, Christie E, Ahern D, Chhabildas VS, Danagher H, Marshall J: *A study on the inspiratory flowrate and power required to trigger Flutiform® K-haler®, Qvar® Easi-Breathe®, and Fostair® NEXThaler® breath actuated inhalers*, Respir Drug Del 2018; 2: pp363-368.

7 Wachtel H, Flüge T, Gössl R: *Flow-pressure-energy-power: which is the essential factor in breathing patterns of patients using inhalers?*, Respir Drug Del 2006; 2: pp511-514.

8 Clark AR, Hollingworth AM: *The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers – implications for in vitro testing,* J Aerosol Med 1993; 6: pp99-110.

9 Haidl P, Heindl S, Siemon K, Bernacka M, Cloes R-M: *Inhalation device requirements for patients' inhalation maneuvers*, Respiratory Medicine 2016; 118: pp65-75.

10 Chodosh S, Flanders JS, Kesten S, Serby CW, Hochrainer D, Witek TJ: *Effective delivery of particles with the HandiHaler® dry powder inhalation system over a range of chronic obstructive pulmonary disease severity,* J Aerosol Med 2004; 14: pp309-315.

11 Ghosh S, Ohar JA, Bradley DM: *Peak inspiratory flowrate in chronic obstructive pulmonary disease: implications for dry powder inhalers,* J Aerosol Med Pulm Drug Del 2017; 30: pp381-387.

12 Medicines & Healthcare products Regulatory Agency (MHRA): *Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule (tiotropium bromide),* Public Assessment Report (PAR) Decentralised Procedure August 2016: 28pp. www.mhra.gov.uk/home/groups/par/documents/websiteresources/con723050.pdf

13 Hochrainer D, Kreher HH, Spallek LS, Wachtel H: *Comparison of the aerosol velocity and spray duration of Respimat® Soft Mist™ inhaler and pressurized metered dose inhalers,* J Aerosol Med 2005; 18: pp273-282.

14 Harris DS, Scott N, Willoughby A: *How does airflow resistance affect inspiratory characteristics as a child grows into an adult?*. (Abstract). Presented at: *The Aerosol Society Drug Delivery to the Lungs 21 Conference, Edinburgh,* Scotland, December 9-11, 2010; J Aerosol Med Pulm Drug Del 2011; 24: pp303-332; DOI: 10.1089/jamp.2011.ab01

15 van Boven JFM, Cushen B, Sulaiman I, Greene G, MacHale E, Mokoka MC, Doyle F, Reilly RB, Bennett K, Costello RW: *Personalising adherence-enhancing interventions using a smart inhaler in patients with COPD :an exploratory cost-effectiveness analysis*, Prim Care Respir Med 2018; 28: Art 24, 3pp DOI: 10.1038/s41533-018-0092-8.