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ORIGINAL ARTICLE

Effect of Human Error, Inhalation Flow, and Inhalation Volume on Dose Delivery from Ellipta® Dry-Powder Inhaler

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Abstract

Purpose Ellipta® is a new dry-powder inhaler (DPI), with medium flow resistance. The present study aimed to evaluate Ellipta® dose preparation and inhalation technique and determine the effect of human factor, inhalation flow, and inhalation volume on total emitted dose (TED).

Methods Two-hundred obstructive lung disease patients were asked to load Ellipta® dose and inhale from placebo Ellipta®, without receiving counseling (first attempt). They were divided into patients who previously used DPI (100 patients) and others who never used DPI before (100 patients). Secondly, TED of single-loaded dose from Relvar-Ellipta® was determined at different inhalation flows (20, 40, and 60 L/min) and inhalation volumes (2 and 4 L). TED was also determined after loading the dose twice at inhalation flows of 40 and 60 L/min and inhalation volume of 4 L. Doses were prepared while Ellipta® is in upright and horizontal positions.

Results The number of handling errors performed by patients who previously used DPI was lower compared to others who never used DPI before. No significant difference was found between TEDs of 40 and 60 L/min inhalation flow at 2 or 4 L inhalation volume when loading Ellipta®, once or twice, in an upright or horizontal position. TED at inhalation flow of 20 L/min was significantly lower than at 40 and 60 L/min ($p < 0.001$). A 4-L inhalation volume significantly increased TED than 2 L/min only at inhalation flow of 20 L/min ($p = 0.001$).

Conclusions Ellipta® is a consistent DPI. It can be used to deliver inhaled medication at a flow of ≥ 40 L/min without fear of not receiving the needed dose. It does not allow delivering double dosing.

Keywords Ellipta® · Human error · Inhalation flow · Inhalation volume · Total dose emitted

Introduction

Dry-powder inhaler (DPI) is an efficient aerosol delivery method for obstructive lung disease patients. It overcomes the metered dose inhaler (MDI) coordination problem but requires the patient to be able to inhale as fast and as deep as possible [1]. Different DPIs are available in the market with different inhalation flow resistance [2]. Each one has a unique method to load the dose and needs critical inhalation flow to deliver the dose [3–5]. They also have different patient preferences and numbers of handling errors [3–5]. The more comfortable the DPI to handle, the more preferred it is by the patient and the physician [6].

DPIs have a very determining step in dose delivery which is to inhale as fast and as deep as possible [3–5]. Some chronic obstructive lung disease (COPD) patients cannot reach sufficient inhalation flow or inhalation volume that allows them to receive the needed dose from the DPI [7, 8]. Also, the patient might inhale double the needed dose if he loaded the DPI twice [9]. This could put the patient at risk of unneeded side effects.

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Ellipta® is a new multi-dose DPI with a medium inhalation flow resistance. It was shown to be very easy to handle and very efficient for pulmonary drug delivery [10–13]. It consists of two rolled up blister strips in which the drug is formulated in 30 individual doses of inhaled medication ready for administration once the dose is prepared. [14] As shown in Fig. 1 adopted form GSK website [15], the design of the Ellipta® decreases the possibility of drug interactions since the blisters containing the medication are separated and open only when the dose is to be inhaled. [14] It was designed to prevent double dosing since it contains a reservoir for any extra dose left behind uninhaled in the blister [14]. Ellipta® was shown to have consistent dose delivery across a range of patient inhalation profiles [12] so there's no need to inhale twice from the same dose as recommended for other DPIs. [4, 5]

Even though Ellipta® was shown to have a low number of handling error and preferred more by the patients [10, 11, 13], there were some, previously found, handling errors that could result in inconsistency of delivered dose or possibly double dosing, e.g., failure to hold device in the right position [10] turned the inhaler upside down after loading a dose [13] or even played with the cover [13]. Those handling error cannot be considered as device errors but they could be considered as human errors. These human errors could result in patient having the medication in hand but cannot correctly receive therapy [16]. These human errors are a tough obstacle in patient counseling regarding inhalation technique of DPIs and MDIs, e.g., inhaling slowly when using MDI and inhaling fast when using DPI [17–19].

Hence, the present study aims to evaluate Ellipta® dose preparation and inhalation technique and determine the effect of human factor, inhalation flow, and inhalation volume on total emitted dose (TED).

Methods

Patients

This part of the study was not designed to determine the efficacy of Ellipta® (GSK, Uxbridge, Middlesex, UK). It was designed to evaluate the Ellipta® dose preparation and inhalation technique of 200 (100 females) adult obstructive lung disease patients, > 18 years old, without verbal or demonstration counseling (first time to see the device). The study was an open-label nondrug interventional study. A local hospital research ethics committee approval number: FM-BSU REC FWA #: FWA00015574 was obtained for the subjects in the study and consents were signed by the obstructive lung disease patients included in the study. They were divided into 100 (50 females) patients who previously used DPI (DPI users) and another 100 (50 females) patients who never used DPI before (DPI non-users).

A placebo Ellipta®, with no medication, was given to each patient. They were asked to prepare the dose and inhale. They were not given any verbal counseling or demonstration on how to use Ellipta®. Errors were reported for each patient when loading Ellipta® according to the recommended Ellipta® inhalation technique [10].

The correct steps of Ellipta® inhalation technique were as follows [10]:

1. Wait to open the cover until you are ready to take your dose. Do not shake the inhaler.
2. Slide the cover down to expose the mouthpiece. You should hear a click.
3. Breathe out away from the device for as long as you feel comfortable. Hold the inhaler away from your mouth—do not breathe out into the mouthpiece.
4. Put the mouthpiece between your lips, and close your lips firmly around it. Do not block the air vent with your fingers.

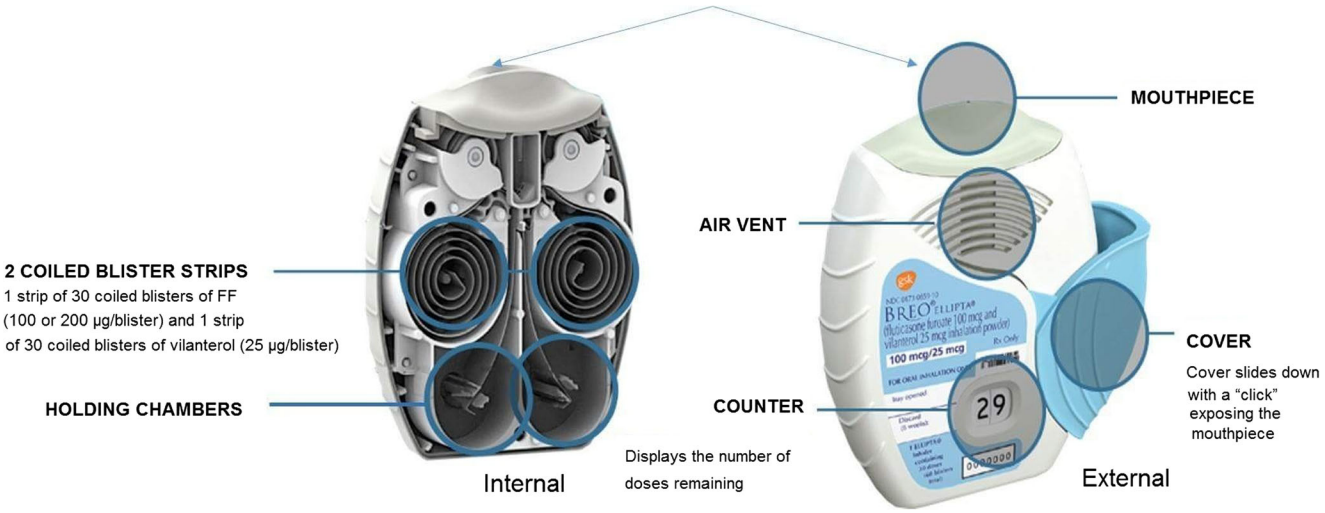

Fig. 1 Design of internal and the external parts of Ellipta [15]

5. Take one long, steady, deep breath in through your mouth.
6. Hold your breath for at least 5 s.
7. Remove the inhaler from your mouth. Breathe out slowly and gently from the nose.
8. Slide the cover upwards as far as it will go, to cover the mouthpiece.

In Vitro Determination of Effect of Inhalation Flow, Inhalation Volume, and Human Error on Total Emitted Dose

Relvar Ellipta® (GSK, Uxbridge, Middlesex, UK) contained 100 μg of fluticasone furoate and 25 μg of vilanterol trifenatate.

The total emitted dose (TED) from a single-loaded dose of Relvar Ellipta® was determined at different inhalation flows (20, 40, and 60 L/min) and different inhalation volumes (2 and 4 L) using DPI sampling apparatus (Copley Scientific Ltd., Nottingham, UK). The patient misuse of Ellipta®, while preparing the dose, was also evaluated by holding the Ellipta® in either upright or horizontal position and loading it to deliver a single dose in each determination according to the instructions in the patient information leaflet. The TED of five separate single doses throughout the life of the inhaler was determined ($n = 5$), for each inhalation flow with different settings.

To investigate the possibility of double dosing, the dose of the Relvar Ellipta® was prepared twice by sliding the cover down to expose the mouthpiece twice while the device in an upright or horizontal position. TED was determined at inhalation volume of 4 L and different inhalation flows (40 and 60 L/min) using DPI sampling apparatus. Each TED separate determination setting was repeated five times throughout the life of the inhaler ($n = 5$).

The inhalation flow through the mouthpiece of the Ellipta® was set at the tested flow (20, 40, or 60 L/min) using a vacuum pump (Brook Crompton, UK). The electronic digital flow meter (MKS Instruments, USA) was used for measuring inhalation flow. In order to allow an inhaled volume of 4 L of air to be drawn through the Ellipta®, flow durations used were 12, 6, and 4 s with the inhalation flow 20, 40, and 60 L/min, respectively. To allow an inhaled volume of 2 L of air at different inhalation flows to be drawn through the Ellipta®, flow durations used were 6, 3, and 2 s, respectively. The apparatus was sealed with parafilm M laboratory film (Pechiney Plastic Packaging, USA). Ellipta® was inserted tightly into the mouthpiece of the DPI sampling apparatus. After each TED determination, the sampling unit was washed with a mixture of methanol and acetonitrile (50:50 *v*/*v*). Also the filter within the sampling unit was entirely submerged in a mixture of methanol and acetonitrile (50:50 *v*/*v*) and then sonicated for 3 min in order to collect all drug entrained on the filter [5].

High-performance liquid chromatography (HPLC) was used to determine the amount of fluticasone furoate, and vilanterol trifenatate deposited in the DPI sampling apparatus after each determination [20]. The HPLC method detected and separated both drugs in the same chromatogram.

HPLC (Agilent 1260 Infinity) with UV detector (Agilent 1260 infinity diode array detector VL (G131SD)) was set at 254 nm. A mobile phase consisted of (50:40:10 *v*/*v*) methanol-acetonitrile-1% sodium perchlorate at pH 4.8, was pumped at a flow rate of 1 ml/min by Agilent 1260 Infinity preparative pump (G1361A), through a c18 column (a 25 mm × 4.6 mm ZORBAX Eclipse Plus, Agilant, USA) with 100 μL.

Statistical Analysis

Analysis of the first part of the study was performed using one way analysis of variance (ANOVA) in conjunction with the post-hoc Tukey's test (SPSS 20 software program, SPSS Inc., Chicago, USA) to find out any possible impact of age (≤ 18 to 40 years old and < 40 years old), gender (male and female), and DPI previous experience (DPI users and DPI non-users) on the total number of correct achievement.

Chi-square test was used to find out any possible impact of age (≤ 18 to 40 years old and < 40 years old), gender (male and female), and DPI previous experience (DPI users and DPI non-users) on the results of each step.

For the second part of the study, all data are expressed as mean (SD). The effect of inhalation flow, inhalation volume, loading positioning, and loading the dose twice were determined using two-way analysis of variance (ANOVA) test using SPSS V15.0 (SPSS Inc., Chicago, USA).

Results

One-hundred (50 females) obstructive lung disease patients were recruited into each group. Their mean (SD) age, weight, and height were 48.9 (14.1) years, 73.7 (11.6) kg, and 168.5 (10.2) cm, respectively for the DPI user group and 47.6 (13.5) years, 78.4(9.4) kg and 172.4(9.6) cm, respectively for DPI non-user group. Table 1 shows the number of correct achievement of each step of the Ellipta® inhalation technique in both studied groups. No significant effect of age or gender was found on the number of correct achievement of Ellipta® inhalation technique or the results of each step. The total number of correct achievement of the Ellipta® inhalation technique was significantly high in DPI user than DPI non-users ($p < 0.001$). There was a significant difference in all the steps between DPI user and DPI non-users ($p < 0.001$) except the first step "Wait to open the cover until you are ready to take your dose. Do not shake the inhaler" ($p = 0.059$). Some steps were tough to be performed correctly without verbal or

Table 1 Number of correct achievement of each step of the correct Ellipta® inhalation technique in obstructive lung disease patients (a) DPI users and (b) DPI non-users groups

Recommended steps	DPI users	DPI non-users
1. Wait to open the cover until you are ready to take your dose. Do not shake the inhaler	100	95
2. Slide the cover down to expose the mouthpiece. You should hear a click.	100	80
3. Breathe out away from the device for as long as you feel comfortable. Hold the inhaler away from your mouth—do not breathe out into the mouthpiece	95	75
4. Put the mouthpiece between your lips, and close your lips firmly around it. Do not block the air vent with your fingers	100	30
5. Take one long, steady, deep breath in through your mouth	90	20
6. Hold your breath for at least 5 s	65	0
7. Remove the inhaler from your mouth. Breathe out slowly and gently from the nose	95	5
8. Slide the cover upwards as far as it will go, to cover the mouthpiece	100	30
Total correct achievement	745	335

demonstration counseling for those who never used DPI before, e.g. "Hold your breath for at least 5 seconds" and "Remove the inhaler from your mouth. Breathe out slowly and gently from the nose.". Some DPI non-users rotated the device in a downward position (seven subjects); some (five subjects) played with the cover (opening more than one time).

The mean (SD) total emitted dose (TED) in micrograms of fluticasone furoate, and vilanterol trifenatate at different inhalation flows and volumes are presented in Tables 2 and 3, respectively. The TEDs of fluticasone furoate and vilanterol trifenatate at an inhalation flow of 20 L/min were significantly lower than 40 and 60 L/min ($p < 0.001$). A 4-L inhalation volume significantly increased the TED than 2 L/min at inhalation flow of 20 L/min only ($p = 0.001$).

No significant difference was found when loading the Ellipta® in the upright (the recommended position in the pamphlet) or horizontal position. No significant difference was found in the TEDs of 40, and 60 L/min inhalation flow at 2 L or 4 L inhalation volume. No significant difference was found in the TED when preparing the dose once or twice.

Discussion

In the present study, subjects who have previously used DPI handled Ellipta® easily compared to those who never used DPI before. That could be due to their previous knowledge of DPI which would help them expect the correct steps. The only step, in DPI user group, with a low number of correct achievement, was the "Hold your breath for at least 5 seconds." A high number of patients using DPI or MDI previously committed this mistake which was improved by continuous verbal counseling [17–19] and even improved more by adding training devices to the counseling [17, 21].

Subjects who never used DPI before showed a higher number of mistakes. Similar to other DPIs, these mistakes would be expected to decrease by verbal counseling on inhalation technique [17, 19].

Some DPI non-users (seven patients) rotated the device in a downward position; some (five patients) played with the cover (opening more than one time), similar to previous studies [10, 11, 13]. These mistakes are very determining since they might affect the delivered dose [22]. That was why we extended the work to TED determination with some intended human errors while loading the dose to check if they would affect Ellipta® TED. However, preparing the dose in horizontal or upright positions did not significantly affect the TED at any inhalation flow or volume. Therefore, no fear of dose loss would be expected while loading Ellipta® dose horizontally or upright position. This would make mistakes like "to hold device in the right position" [10] and "turned the inhaler upside down after loading a dose" [13] cause no problem in dose delivery.

Inhalation flow of 20 L/min delivered significantly the lowest ($p < 0.001$) TED which was also significantly affected by the inhaled volume ($p < 0.001$). Similar to DPI with low and medium resistance (Aerolizer and Diskus, respectively) [23],

Table 2 The mean (SD) total emitted dose (μg) of 100 μg fluticasone furoate at different inhalation flows, volumes, and positions

Volume	Single dosing						Double dosing			
	20 L/min		40 L/min		60 L/min		40 L/min		60 L/min	
	Horizontal	Upright	Horizontal	Upright	Horizontal	Upright	Horizontal	Upright	Horizontal	Upright
4 L	72.6(24.8)	64.9(27.6)	90.4(9.3)	96.0(5.2)	96.9(4.0)	100.7(2.1)	97.3(6.4)	101.7(1.6)	101.0(0.7)	99.0(1.1)
2 L	54.8(19.4)	49.6(22.0)	93.2(3.4)	97.2(3.2)	97.7(0.9)	96.5(0.4)	–			

Table 3 The mean (SD) total emitted dose (μg) of 25 μg vilanterol trifenatate at different inhalation flows, volumes, and positions

Volume	Single dosing						Double dosing			
	20 L/min		40 L/min		60 L/min		40 L/min		60 L/min	
	Horizontal	Upright	Horizontal	Upright	Horizontal	Upright	Horizontal	Upright	Horizontal	Upright
4 L	18.2(6.2)	16.2(6.9)	22.6(2.3)	24.0(1.3)	24.2(1.0)	25.2(0.6)	24.3(1.6)	25.4(0.4)	25.2(0.2)	24.8(0.3)
2 L	13.7(4.9)	12.4(5.5)	23.3(0.9)	24.3(0.8)	24.4(0.2)	24.1(0.1)	–			

TEDs at 40 L/min and 60 L/min inhalation flow were similar whatever the inhalation volume was (2 or 4 L).

Most DPIs, primarily the highly flow-resistant ones, are strongly affected by the inhalation flow and inhaled volume [3–5]. Therefore, some DPIs are not suitable for obstructive lung disease patients or young age children. Some DPI studies recommended inhaling twice from the same dose for better delivery [3–5]. The medium resistance of the Ellipta® to inhalation flow [14] overcame the need to inhale twice from the same dose and reduce the effect of inhalation volume [23]. However, we still can say that the more inhalation flow and volume the patients can perform through the Ellipta®, the better the delivered dose and the more consistent the TED. This is observed in the very low standard deviation of the TED at inhalation flow 60 L/min compared to the 40 and 20 L/min inhalation flow suggesting more consistency at high flow [12]. Furthermore, the highest delivered dose from Ellipta® was about 101.7% of the nominal dose at inhalation flow of 40 L/min.

Comparing the results of the present study to a similar study with another DPI (Turbuhaler), as an example of highly resistant DPI [9] at 40 L/min, TED from Turbuhaler was not more than 50% delivered from nominal dose. A 100% delivered dose was at inhalation flow of 90 L/min which cannot be performed by many COPD patients [9]. The delivered dose in the Turbuhaler study had a high standard deviation at all inhalation flow tested [9]. Additionally, Turbuhaler in Tarsin et al. study resulted in about 133% delivered dose, compared to 101.7% by Ellipta® in the present study. Tarsin et al. rationalized the Turbuhaler excess 33% delivered at 90 L/min inhalation flow by the left over medication in the inhalation chamber [9].

The present study shows that preparing the dose once or twice resulted in no left over medication in the Ellipta® inhalation chamber. This, in addition to the low standard deviation, show how consistent the Ellipta® compared to other DPI with which preparing the dose twice would put the patient at a possibility of inhaling left over medication or double doses. [14]

So, to deliver 100% of the nominal dose, the patient has to inhale at flow of 90 L/min from Turbuhaler [9] and 40 L/min from Ellipta®. Even at 20 L/min inhalation flow, the Ellipta® TED was around 60% at 2 or 4 L inhalation volume. This adds an advantage to the Ellipta® since the patient with severe obstructive lung disease can perform this inhalation flow and volume [24]. However, we still recommend patients to follow the dose preparation recommended [10] and inhale as fast and as deep as possible for better delivery.

Conclusions

Ellipta® is an easy-to-handle device among patients who previously used other DPIs but still need verbal counseling to patients who never used other DPI before.

Patients can prepare the dose while holding the Ellipta® in the upright or horizontal position with no fear of delivery failure. Inhalation volume has no effect on TED especially at inhalation flow ≥ 40 L/min, which patients are encouraged to perform when using any DPI. No possibility of double dosing or inhaling left over medication could happen with Ellipta® even if the device was loaded twice.

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