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The impact of inspiratory effort on inspiratory flow through Turbuhaler® in asthmatic patients

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The impact of inspiratory effort on inspiratory flow through Turbuhaler® in asthmatic patients. G. Persson, B. Olsson, S. Soliman. ©ERS Journals Ltd 1997.

ABSTRACT: To investigate the impact of the inhalation effort on the peak inspiratory flow through Turbuhaler®, 100 asthmatics having a wide range of asthma severity (baseline forced expiratory volume in one second 28–127% of predicted normal) were studied. Each patient inhaled through four modifications of empty Turbuhaler inhalers, using first a "deep" inhalation and then a "forceful and deep" inhalation manoeuvre.

Peak inspiratory flow increased by an average of 20% using a "forceful and deep" as compared to a "deep" inhalation, with a markedly higher increase for the patients who had a low peak inspiratory flow using the deep inhalation. Virtually all patients (97–100%) attained a peak inspiratory flow ≥40 L·min^{-1} after a "forceful and deep" inhalation.

This study demonstrates that instructing the patient to take a "forceful and deep" inhalation optimizes the use of Turbuhaler®. Irrespective of asthma severity, the vast majority of patients could attain a sufficiently high peak inspiratory flow with a "forceful and deep" inhalation.

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Considerable improvement of asthma therapy was accomplished with the introduction of chlorofluorocarbon-propelled pressurized metered-dose inhalers (pMDIs). As a further improvement of inhalation therapy, dry powder inhalers (DPIs) were developed to overcome problems associated with the use of pMDIs [1–5].

All current DPIs are breath-actuated, which provides an inherent co-ordination between inhalation and drug release. Thus, the function of DPIs depends on a flow of air through the inhaler. Up to a certain level, a higher inspiratory flow through a DPI enhances drug delivery and gives better deaggregation of the drug particles [6, 7], thus resulting in better lung deposition [8–10]. For pMDIs, on the other hand, the flow relationship appears to be the reverse; a higher inspiratory flow has been shown to result in higher deposition in the oropharynx and, consequently, a lower lung deposition [11, 12].

Turbuhaler® is a multidose, dry powder inhaler, which delivers an aerosol of micronized drug [13]. The original version of inhalation instructions, which was based on the experiences gained from using pMDIs, told the patients to take a deep inhalation from the inhaler without emphasis on the use of force during inhalation. This instruction was later revised, according to clinical experience and experimental data on using Turbuhaler, to ask for a forceful and deep inhalation.

This study compared the impact of the old and new instructions on the inspiratory flow through Turbuhaler in asthmatic patients. To get a differentiated picture of the impact of flow resistance on the inspiratory airflow, the investigation utilized four modifications of inhalers spanning that of the commercially available products.

Patients and methods

One hundred patients (39 males and 61 females) with asthma, who normally used Turbuhaler according to the original instruction, entered and completed the study. They had a mean age of 42 yrs (range 16–77 yrs), and a wide range of asthma severity, and their baseline forced expiratory volume in one second (FEV_1) varied between 28 and 127% of predicted values. Table 1 summarizes patient demographics.

Before and after performance of the inhalation test, the patients used their ordinary asthma medications as prescribed. The patients gave written informed consent and the study was approved by the Ethics Committee of the University Hospital of Lund, Sweden.

The patients inhaled from four experimental modifications of empty Turbuhaler inhalers (A–D) with different flow resistances. The mean flow resistance, expressed

Table 1. – Demographic details of the patients studied (n=100)

Characteristic		
Age	42±16	(16–77)
Height cm	171±9	(150–193)
Weight kg	72±14	(50–143)
Duration of asthma yrs	16±13	(0.7–68)
FEV_1 L	2.9±0.9	(0.8–5.1)
% pred	87±19	(28–127)
FVC L	3.6±1.1	(1.0–6.5)

Values are presented as mean±SD, and range in parenthesis. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; % pred: percentage of predicted value.

as the square root of the pressure drop over the inhaler at a flow of 60 L·min^{-1} (1 L·s^{-1}), was 66.0, 71.5, 82.7 and 85.4 Pa$^{0.5}$·s·L^{-1} for inhaler A, B, C and D, respectively. The coefficient of variation (CV) was below 3%. The Turbuhaler products currently available have a flow resistance between that of inhaler B and C.

The patients used two different inhalation manoeuvres. The order of inhalers (A–D) was randomized in a single-blind manner. The patients performed both inhalation manoeuvres with the four inhalers on the same day at the clinic.

They were first asked to take a "deep" inhalation through the inhaler, according to the original instruction: 1) Unscrew and lift off the cover; 2) Hold the inhaler upright with the grip downwards. Load the inhaler with a dose by turning the grip as far as it will go and then back to the original position; 3) Breathe out. Do not breathe out through the inhaler; 4) Place the mouthpiece between your teeth, close your lips and "breathe in deeply" through your mouth; 5) Before breathing out, remove the inhaler from your mouth. If more than one dose has been prescribed, repeat steps 2–5; 6) Replace the cover.

The patients were then asked to repeat the inhalation through the four inhalers after being instructed to inhale "forcefully and deeply", according to the new instruction (in which all steps, except step 4, are the same as in the original instruction): 4) Place the mouthpiece between your teeth, close your lips and "breathe in forcefully and deeply" through your mouth.

The inhalation flow curves were recorded by connecting the inhaler to a Vitalograph® Spirometer. Peak inspiratory flow through the inhaler (PIFINH), inspired volume, time to reach PIFINH, and time to reach 75% of PIFINH were evaluated from the flow curves.

Statistics

PIFINH inspired volume, time to reach PIFINH, and time to reach 75% of PIFINH, are presented as means and standard deviations (or CV). A paired t-test was used for comparing the two inhalation manoeuvres. A two-factor analysis of variance (ANOVA) test was used to compare the inhaler modifications. A p-value of less than 0.05 was considered significant.

Results

Peak inspiratory flow through the inhalers

When the patients inhaled according to the old instruction, using a "deep" inhalation, they achieved a mean PIFINH that was inversely related to the flow resistance of the inhaler, and ranged 53–65 L·min^{-1} for inhalers A–D (table 2). After instructing the patients to inhale "forcefully and deeply", the mean PIFINH ranged 62–78 L·min^{-1}, an increase of approximately 20% for all inhaler modifications. The CVs were reduced from approximately 30% after the "deep" inhalation to approximately 20% after the "forceful and deep" inhalation.

Table 2. – Peak inspiratory flow through inhalers A–D (PIFINH) (n=99–100)

Inhaler	Peak inspiratory flow "Deep" inhalation Mean	CV	"Forceful & deep" inhalation Mean	CV	Improvement after change from "deep" to "forceful & deep"
	L·min^{-1}	%	L·min^{-1}	%	%
A	65.4	29	78.0	19	19
B	61.0	31	73.6	20	21
C	54.5	28	65.1	19	19
D	52.9	29	62.2	20	18

CV: coefficient of variation.

The difference in PIFINH between the two manoeuvres was highly significant ($p<0.0001$).

The increase in PIFINH obtained after being given the new instruction was found to be inversely related to the patient's initial PIFINH. Table 3 presents a subdivision of the patients into five groups according to their initial PIFINH after the "deep" inhalation (data for inhaler C). The largest increase was obtained in the subgroup (No. 1) which had the lowest PIFINH with the original instruction, whereas the subgroup (No. 5) with the highest initial PIFINH showed no change. Equivalent results (not shown) were obtained for the other inhaler modifications (A, B and D).

The impact of the two inhalation manoeuvres on inspiratory flow through the inhaler can also be compared by studying the distribution of patients with certain levels of PIFINH. Table 4 shows the accumulated percentage of patients with PIFINH values below 30, 40, 50 and 60 L·min^{-1}, and the remaining percentage with PIFINH ≥60 L·min^{-1}, for each inhaler during both inhalation manoeuvres. The instruction to perform a "forceful and deep" inhalation reduced the number of patients with low PIFINH. For example, virtually all patients (97%) had a PIFINH ≥40 L·min^{-1} after the "forceful and deep" inhalation from inhaler C. The corresponding figure after the "deep" inhalation was 86%. The majority of patients (67%) achieved a PIFINH ≥60 L·min^{-1} after inhaling forcefully and deeply from inhaler C.

Table 3. – Improvement in peak expiratory flow through inhalers A-D (PIFINH) after changing to "forceful and deep" inhalation for different subgroups classified according to their initial PIFINH after "Deep" inhalation (data for inhaler C)

Subgroup No.	Initial PIFINH	Pts	Mean PIFINH "Deep" inhalation	"Forceful inhalation & deep"	Improvement after change from "deep" to "forceful & deep" inhalation
	L·min^{-1}	n	L·min^{-1}	L·min^{-1}	%
1	≤43	20	35	57	63
2	44–54	19	50	66	32
3	55–66	20	60	75	25
4	67–79	20	72	79	10
5	≥80	20	88	88	0

Pts: patients.

Table 4. – Accumulated percentage of patients below certain PIFINH

Type of inhaler	"Deep" inhalation with PIFINH L·min^{-1}					"Forceful & deep" inhalation with PIFINH L·min^{-1}				
	<30 %	<40 %	<50 %	<60 %	≥60 %	<30 %	<40 %	<50 %	<60 %	≥60 %
A	4	12	20	39	61	0	0	6	14	86
B	4	13	27	52	48	0	1	7	19	81
C	6	14	38	64	36	0	3	13	33	67
D	6	16	41	67	33	1	3	14	44	56

PIFINH: peak inspiratory flow through inhaler.

Time to reach PIFINH and inspired volume

It took a mean (SD) time of 0.75 (0.42) s to reach PIFINH with the "deep" inhalations, and 0.58 (0.28) s with the "forceful and deep" inhalations. The initial phase of the inhalation can be characterized by the time to reach a set fraction, *e.g.* 75%, of the peak flow. The mean (SD) time to reach 75% of the peak flow was 0.23 (0.13) s with the "deep" inhalations, and 0.19 (0.11) s with the "forceful and deep" inhalations. The difference between inhalation manoeuvres was highly significant ($p<0.0001$). There was no significant difference between the inhaler modifications.

The mean (SD) inspired volume with the "forceful and deep" inhalations, 2.6 (1.1) L, was significantly larger than with the "deep" inhalations, 2.1 (1.0) L ($p<0.0001$). The inspired volume was approximately the same (±0.1 L) for the different inhaler modifications.

Discussion

Asthma is an inflammatory disease of the airways, characterized by increased expiratory airway resistance and airway hyperreactivity. In contrast, inspiratory flow is less affected by asthma and is primarily dependent on the force employed during the manoeuvre and on extrapulmonary limitations, such as tracheal stenosis [14] or the resistance of an inhaler [7, 15]. Inspiratory flow is, therefore, poorly correlated to expiratory parameters, and even severely obstructed asthmatics can produce normal or near-normal inhalations through Turbuhaler [16, 17].

This study was performed to document the impact of two different instructions on the inspiratory flow through Turbuhaler in patients with asthma. The results demonstrated that the instruction to use a "forceful and deep" inhalation elevated the mean PIFINH by approximately 20%, as compared with the instruction to use a "deep" inhalation, irrespective of the flow resistance over the inhaler. As expected [7, 15,] PIFINH was inversely related to the flow resistance for both manoeuvres. It was further shown that the coefficient of variation of inspiratory flow rate was reduced by using a "forceful and deep" inhalation manoeuvre. Moreover, the instruction to use force shortened the time to reach the peak flow and increased the inspired volume for all four inhaler modifications. The relative effect of inhalation instructions was, thus, the same, irrespective of the flow resistance of the inhaler. The positive effect of the instruction to inhale "forcefully and deeply" was most pronounced in patients who performed a low PIFINH following the instruction to inhale "deeply". The inhalation technique of these patients could, thus, be considerably improved by the more informative instructions. This shows that a low PIFINH by these patients was due more to a suboptimal effort following inadequate instructions than to physiological limitations.

This investigation utilized empty inhalers and, hence, no efficacy data were obtained. There is probably no strict limit between what may be considered a sufficient and a suboptimal inspiratory flow through Turbuhaler for efficacious drug delivery. Studies have demonstrated that at typical flow rates through Turbuhaler, around 60 L·min^{-1}, both lung deposition and clinical efficacy of budesonide, terbutaline, salbutamol and ipratropium bromide are about twice that obtained *via* the corresponding pMDI [18–22]. Furthermore, it has been shown that a reduction of inspiratory flow from 60 to about 30–40 L·min^{-1} lowers the lung deposition of budesonide and terbutaline by approximately 50% [8, 9], probably as a consequence of a decrease in the fine particle dose emitted from the inhaler [6, 7]. This indicates that at a peak flow of about 30–40 L·min^{-1} through Turbuhaler, the efficacy may be reduced to that of an optimally used pMDI. It has, however, been demonstrated for terbutaline that Turbuhaler retains its efficacy down to a flow rate of 30 L·min^{-1} [23, 24]. The present data showed that virtually all patients attained a PIFINH above this range when instructed to inhale "forcefully and deeply", indicating that the vast majority of patients can attain a sufficiently high PIFINH to ensure efficacious drug delivery. Hence, in the light of previous data suggesting that inhalation flow rate is one of the critical determinants of the amount of the drug deposited in the airways, this study suggests that clear and precise instructions, emphasizing the use of a forceful and deep inhalation, should be given to patients using Turbuhaler.

In conclusion, instructing the patient to take a "forceful and deep" inhalation optimizes the use of Turbuhaler. Virtually all patients attained a peak inspiratory flow through Turbuhaler of at least 40 L·min^{-1}.

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