Pressure and inspiratory flow characteristics of dry powder inhalers

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Summary This study compared inspiratory characteristics of the Novolizer® and Turbuhaler®. Sixty patients with obstructive lung disease (40 asthmatics, 20 patients with COPD) and without DPI experience were enrolled into this investigator initiated, randomized, cross-over study. Collected data of 56 patients were eligible for analysis. Inspiratory pressure and inspiratory flow through both devices were measured in every patient using a double-beam oscilloscope. Peak inspiratory flow (PIF), duration of inspiratory flow >60 l/min and increase in inspiratory pressure were significantly higher in the Novolizer® group. In addition, the inspiratory flow rate 0.1 s after beginning of inhalation was over two-times higher at inhalation through the Novolizer® compared to inhalation through the Turbuhaler®. The Turbuhaler® data, but not the Novolizer® data, showed a significant negative correlation between lung function and inspiratory flow. The dynamic resistance of the Turbuhaler® was 5.5-times higher than that of the Novolizer®. Patients using the Turbuhaler® had to invest a significantly higher inspiratory effort compared to the use of the Novolizer® in order to achieve the same inspiratory flow (e.g., 60 l/min). Indeed, more than 40% of the patients in the Turbuhaler® group failed to reach an inspiratory flow of 60 l/min. Overall, patients inhaling through the Novolizer® had a better inhalation performance than those inhaling through the Turbuhaler®.

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Introduction

The choice of inhaler device should be an integral part of obstructive lung disease management decisions. Pressurized metered-dose inhalers (pMDIs) are the most popular devices for administering drugs for inhalation. However, more than 80 countries have signed the Montreal Protocol to ban the production of chlorofluorocarbons (CFCs) in the next few years1 which necessitates the replacement of CFC-propelled pMDIs with other aerosol delivery devices. Among the alternative means of delivering therapeutic aerosols, dry powder inhalers (DPIs) are gaining popularity and acceptance. Crystalline or powder drugs for inhalation are inexpensive, do not depend on the use of CFC and do not require coordination between inhalation and device activation. Recent improvements in the design, ease of use, and multidose capability make DPIs attractive alternatives to pMDIs for aerosol therapy in patients with asthma.2

For the delivery of a therapeutic agent from an inhalation device to the lungs, a high quality aerosol with a small particle size (diameter 2–5 μm) must be generated. If the particles are larger than that, they are deposited in the upper airways and in the mouth. If they are smaller, they cannot be deposited in the lungs, therefore they are exhaled. With pMDIs, the energy required to aerosolize drug

Abbreviations: CFC, chlorofluorocarbon; DPI, dry powder inhaler; FEV₁, forced expiratory volume in 1 s; FPF, fine particle fraction; P₀.₁, inspiratory flow at 0.1 s post-inhalation; PIF, peak inspiratory flow; pMDI, pressurized metered dose inhaler
particles within the device ready for inhalation by the patient is propellant-generated. However, with DPIs the drug powder must be desagglomerated into respirable particles. The initiation of this starts with the inhalation procedure itself (i.e., the pressure and flow that a patient generates through the device during the inhalation maneuver). In fact, doubling the inspiratory velocity quadruples the energy generated.

There are several dry powder inhaler devices on the market, characterized as single dose devices or multiple dose devices based on a reservoir system or premetered doses. The Novolizer® (VIATRIS, Frankfurt, Germany) and the Turbuhaler® (AstraZeneca, Lund, Sweden) are two reservoir multiple dose dry powder inhalers (MDPIs), both of which deliver the inhaled corticosteroid budesonide. However, the intrinsic resistance of the Turbuhaler® is higher than that of the Novolizer®. The aim of this study was to compare inspiratory characteristics as well as inspiratory characteristic reproducibility of the Novolizer® and the Turbuhaler® in patients without DPI experience and to assess the effect of time point of instructions for use on patient performance.

Materials and methods

Patients

Sixty patients with obstructive lung disease (40 asthmatics and 20 COPD patients) were enrolled into the study. None of the patients had used a dry powder device previously, but used a pMDI or no inhalative asthma therapy. Collected data of 56 patients were eligible for analysis. Patient characteristics are shown in Table 1. Patients gave their written informed consent before being enrolled into the study.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient baseline characteristics.</th>
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<tr>
<td>Patient characteristics</td>
<td></td>
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<tr>
<td>Sex</td>
<td>30 male, 30 female</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.9 ± 19.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.5 ± 17.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.7 ± 9.1</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>79.6 ± 20.1</td>
</tr>
<tr>
<td>P_{imx} (kPa)</td>
<td>9.7 ± 9.3</td>
</tr>
<tr>
<td>P_{0.1} (kPa)</td>
<td>0.3 ± 0.2</td>
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</table>

Results are presented as mean±standard deviation.

Study design

This investigator-initiated study had a randomized cross-over design. Before starting data collection, patients received instructions according to the instructions for use brochures for both the Turbuhaler® and the Novolizer®. In both cases a placebo inhalation device without the relevant drug formulation (i.e., budesonide) was used. Every patient inhaled at least two times through each of the two devices in randomized order. The following flow and pressure variables were measured for each device using a double-beam oscilloscope (Velleman Storage Scope for PC, sampling rate 20MHz), Spiroceptor (Siemens) plugged to an Ellison pressure transducer (ESI, UK), Keller pressure sensor (Keller, Switzerland) (Fig. 1); peak inspiratory flow (PIF; l/s); time to peak inspiratory flow (s); inspiratory flow at 0.1 s post-inhalation (P_{0.1}; l/s); duration of inspiratory flow >30 l/min and >60 l/min (s) respectively; peak inspiratory pressure (kPa); and time to peak inspiratory pressure (s). A first and second inspiratory maneuver was performed with the Novolizer® and the Turbuhaler®, respectively, recording peak inspiratory pressure, time to PIF and time taken to reach an inspiratory flow plateau in order to check for reproducibility. The inspiratory characteristics of time to PIF, PIF, peak pressure and duration of inspiratory flow >60 l/min were correlated with the lung function variables forced expiratory volume in 1s (FEV1, %predicted) and the ratio of P_{0.1} and PIF.

Inhalation characteristics before and 6 weeks after instruction were also recorded for both the Novolizer® and the Turbuhaler®.

Statistics

Inspiratory characteristics of the devices, dynamic resistance and within device reproducibility of inspiratory characteristics were compared using the Wilcoxon matched pairs test. Patient performance with each device before and 6 weeks after instruction was analysed using a combined t-test. P-values ≤0.05 were judged to be significant.

Results

Inspiratory characteristics

Figure 2 shows an inspiratory flow and pressure trace for both devices. For the Novolizer®, peak inspiratory pressure was achieved at approximately 10 cm H2O when patients noticed the acoustic
feedback, the PIF was just over 60 l/min at this pressure. However, a much higher inspiratory pressure was required through the Turbuhaler (approximately 70 cm H₂O), and the PIF of 60 l/min was not completely reached at that pressure.

Inspiratory flow and pressure characteristics are summarized in Table 2. The PIF, duration of inspiratory flow > 60 l/min and increase in inspiratory pressure were all statistically significantly higher in the Novolizer group compared to the Turbuhaler group (Table 2). Patients in the Novolizer group attained a PIF through the device of approximately 80 l/min compared with just 55 l/min for the Turbuhaler group. In this study on patients without DPI experience using both devices for the first time, eight patients (14.3%) in the Novolizer group and 25 patients (44.6%) in the Turbuhaler group failed to attain an inspiratory flow rate of 60 l/min. Therefore, almost half of these patients were unable to use the Turbuhaler in an optimal way. By contrast, all patients inhaling through the Novolizer were capable of generating an inspiratory flow rate of min 30 l/min, but 5 patients (5.4%) in the Turbuhaler group failed to reach even this inspiratory flow rate. In terms of \( P_{0.1} \), the patients in the Novolizer group had more than double the inspiratory flow rate of those in the Turbuhaler group.

**Correlation with lung function**

There was no correlation between PIF, time to PIF, peak inspiratory pressure or flow duration of PIF > 60 l/min and FEV₁ (% predicted) for either the Novolizer or the Turbuhaler group. Similarly, none of the inspiratory characteristics measured through the Novolizer significantly correlated with \( P_{0.1}/\text{PIF} \) ratio. However, there was a significant correlation between \( P_{0.1}/\text{PIF} \) and both PIF (\( P < 0.0001 \)) as well as time at which inspiratory flow was > 60 l/min (\( P < 0.011182 \)) for the Turbuhaler group.

**Inspiratory characteristics reproducibility and device resistance**

The reproducibility of the inhalation in the same patient using the same device did not show any statistically significant differences for the Novolizer or the Turbuhaler for the variables of peak pressure, time to PIF and time to inspiratory flow plateau. The dynamic resistance of the
Turbuhaler\textsuperscript{K} was 28.45 cm H\textsubscript{2}O.s/l, 5.5 times higher to that for the Novolizer\textsuperscript{K} (5.07 cm H\textsubscript{2}O.s/l) ($P<0.000001$).

**Effect of patient instruction**

Patients’ inhalation characteristics showed remarkable similarity before instruction and 6 weeks after instruction and did not significantly change during that time for either the Novolizer\textsuperscript{K} or the Turbuhaler\textsuperscript{K} (Table 3).

**Discussion**

This study showed that the patients’ inhalation performance through the Novolizer\textsuperscript{K} was superior to that through the Turbuhaler\textsuperscript{K}. PIF and flow...
duration with PIF > 60 l/min were significantly higher for the Novolizer® group, and intrinsic resistance was significantly lower compared to that of the Turbuhaler®.

Many patients are unable to use their pMDIs correctly. DPIs should be easier to use as they do not require coordination of inhaler activation with inhalation. However, patients without DPI experience and switching from pMDI to DPI tend to apply a similar inhalation maneuver as with a pMDI, and this may result in reduced peak inspiratory flow rates. This aspect needs to be considered when reviewing the results of the present investigation which was conducted on a patient population without DPI experience (pMDI or no inhalation therapy). The Novolizer® offers technical features to these patients which optimize their inhalation maneuver. Unlike the Turbuhaler®, the Novolizer® guides the patient through the inhalation procedure. Pressing down the dosage button initiates premetering of a dose as well as a color change of the indicator window from red to green telling the patient that the device is ready for inhalation. During inhalation, optical, acoustic and sensory feedback mechanisms, with the first two of them being linked to an inspiratory flow rate threshold of 35–50 l/min, inform the patient that inhalation maneuver was correct. A dose counter informs the patient about remaining doses and can be reset for next counting only upon correct inhalation. These features should increase the patient’s trust in DPI use and make it easier to use. This fact was shown in the present study as more patients in the Turbuhaler® group, after reading the instructions-for-use brochure, were unable to use the inhaler and exhaled into the device on at least one occasion before inhalation. This is important as, if patients exhale into the Turbuhaler® before inhalation, the drug is inadvertently released through the air channels of the device and is not available anymore for inhalation.

For all breath-activated devices the fine particle fraction (FPF) is dependent on flow rate. Increasing the flow rate produces a greater amount of drug delivered and increases the respirable fraction from DPIs, the dose which a patient inhales, and hence the effectiveness of the therapeutic agent, depends upon the inspiration capacity. For example, Hirsch and colleagues showed that the effectiveness of terbutaline-induced bronchodilation was dependent on inspiratory capacity through the Turbuhaler®. In the present study, the mean PIF generated by selected patients without DPI experience was 79.8 l/min for the Novolizer® compared with just 54.3 l/min for the Turbuhaler®. A flow rate of 80 l/min through the Novolizer® has previously been shown to correspond to a FPF or respirable fraction of 34% of a 200 μg budesonide dose. Similarly, at a flow rate of 60 l/min through the Pulmicort Turbuhaler®, the FPF generated has been shown to be about 21%. In other words, at the PIF measured in the current study the Turbuhaler® emits about one third less respirable fraction of therapeutic agent (i.e., budesonide) than the Novolizer®.

Flow during the initial part of the inspiratory effort is important in determining the characteristics of the aerosol generated by a DPI. For DPIs, a minimal inspiratory flow must be achieved immediately after the start of the inspiration maneuver as desagglomerate the powder takes place before 0.1 s. In this study the flow rate achieved through the Novolizer® 0.1 s after the start of inhalation was more than double of that achieved through the Turbuhaler® ($P<0.00001$). Therefore, according to the equation $E = dP = \frac{1}{2}PV^2$, the amount of energy generated by patients 0.1 s into

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### Table 3  Peak inspiratory flow and pressure characteristics achieved by patients with obstructive lung disease ($n = 56$) inhaling through the Novolizer® and through the Turbuhaler® before and 6 weeks after instruction.

<table>
<thead>
<tr>
<th></th>
<th>Novolizer®</th>
<th>Turbuhaler®</th>
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<tbody>
<tr>
<td></td>
<td>Before instruction</td>
<td>6 weeks after instruction</td>
</tr>
<tr>
<td>Time to peak pressure (s)</td>
<td>0.44±0.28</td>
<td>0.44±0.25</td>
</tr>
<tr>
<td>Peak pressure (kPa)</td>
<td>6.20±1.04</td>
<td>6.21±0.93</td>
</tr>
<tr>
<td>Peak flow (l/s)</td>
<td>1.30±0.32</td>
<td>1.32±0.33</td>
</tr>
<tr>
<td>Flow time &gt;60 l/min</td>
<td>0.75±0.55</td>
<td>0.77±0.56</td>
</tr>
</tbody>
</table>

Results are presented as mean± standard deviation.
the inhalation maneuver was four times higher for the Novolizer® than for the Turbuhaler®.

The importance of achieving a high inspiratory flow at the start of the inhalation maneuver was demonstrated by Everard and colleagues who showed that with the Turbuhaler®, the rate of increase in flow significantly affected the particle size distribution of the aerosol. Failure to attain a flow rate of 301/min before 150 ml of air had passed through the device resulted in the aerosol median particle diameter increasing from less than 6.6 μm to greater than 45.3 μm. Therefore, particle size and hence the amount of drug delivered to the lung from a DPI is dependent on both patient flow rate and flow profile.

Patients’ lung function may affect how well they can inhale through a device. In the present study only in the Turbuhaler® group inspiratory flow negatively correlated with respiratory muscle strain (i.e., patients with a high P_{0.1}/PIF ratio generated a low PIF and flow duration >60 l/min and vice versa). This is likely due to the high dynamic resistance of the Turbuhaler®. By contrast, no significant correlation was observed between lung function and any inspiratory characteristic in the Novolizer® group, suggesting that it is equally effective in patients with mild disease as well as those with more severe airflow obstruction.

The Novolizer® has been designed to offer low to medium resistance on inhalation. By contrast, the Turbuhaler® has a high intrinsic resistance, requiring a relatively high inspiratory flow of min. 60 l/min for optimal drug delivery. In the present study we found the intrinsic resistance of the Turbuhaler® to be 5.5 times higher than that of the Novolizer®. Patients using the Turbuhaler® must invest a significantly higher inspiratory effort compared to the use of the Novolizer® in order to overcome the DPI’s intrinsic resistance and achieve the same inspiratory flow (e.g., 60 l/min). Close monitoring and repeated training are necessary to ensure that patients continue to use their inhalers correctly. For the delivery of medication to the lungs of patients with obstructive lung disease, it is essential that an inhalation device is chosen which closely matches the needs of the patient. The results of the present study suggest that the Novolizer®, with its low to medium resistance and superior inhalation characteristics, offers more advantages to the “average patient” than the Turbuhaler®.

Conclusions

The present study showed that the instruction-for-use brochure on its own might not be a sufficient tool to train patients on correct DPI use. Every patient needs to be instructed and ideally train with a placebo device without drug powder before starting inhalation therapy. There are important differences between the devices regarding inhalation characteristics. The Novolizer® is a low to medium resistance device. Patients inhaling through the Novolizer® are capable of generating a higher PIF_{0.1} and increase in peak pressure compared to patients inhaling through the Turbuhaler®. In addition, the Turbuhaler® may not be suitable for patients with severe airflow obstruction as the inspiratory flow generated through this device is negatively correlated with patients’ lung function. Patients using the Turbuhaler® must invest a much higher inspiratory effort compared to the use of the Novolizer® in order to overcome the DPI’s intrinsic resistance and achieve the same inspiratory flow (e.g., 60 l/min). Close monitoring and repeated training are necessary to ensure that patients continue to use their inhalers correctly.

For the delivery of medication to the lungs of patients with obstructive lung disease, it is essential that an inhalation device is chosen which closely matches the needs of the patient. The results of the present study suggest that the Novolizer®, with its low to medium resistance and superior inhalation characteristics, offers more advantages to the "average patient" than the Turbuhaler®.

References


