Successful use of DPI systems in asthmatic patients—key parameters

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Summary Effective inhalation therapy using pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) is the cornerstone of asthma management. Previous studies have demonstrated difficulties in the usage of pMDIs in certain patient groups, especially as pMDIs require the co-ordination of inhaler activation with dose inhalation. Almost all DPIs are breath-activated and preclude the need to co-ordinate activation with inspiration. Three key parameters for successful inhaler use should be considered when evaluating existing or future DPI devices: (1) compliance; (2) fine particle distribution and dependency on inspiratory flow and; (3) clinical efficacy. A threshold mechanism which controls for a minimal inspiratory flow rate is desirable in order to support formation of an optimal fine particle fraction (FPF) which in turn improves lung deposition. Additionally, in order to enhance patient compliance an optimal multidose DPI should feature a visual or acoustic feedback of a correct inhalation. The Novolizer® is a multidose refillable DPI. It has multiple feedback mechanisms and a trigger flow valve system, which helps to ensure correct inhalation that allows adequate lung deposition, helps to reassure the patient that medication has been taken and might therefore improve patient compliance. The low-to-medium airflow resistance translates into higher peak inspiratory flow (PIF) and makes the Novolizer® DPI particularly suitable for the use in patients with reduced inspiratory flow rates. Clinical studies have shown that children, elderly patients, adults with moderate-to-severe asthma and COPD patients (stage IIa-III) are able to generate sufficient inspiratory flow to operate the Novolizer® effectively. In contrast previous studies with other MDPIs (e.g. Turbuhaler® or Aerolizer®) demonstrated that in patient groups with severe...
Introduction

The majority of patients with asthma use pressurised metered dose inhalers (pMDIs) to deliver medication to their lungs, but they are often inefficient and difficult to operate. A recent study by Giraud and Roche\(^1\) showed that misuse of pMDIs is frequent and associated with poor asthma control in inhaled corticosteroid (ICS)-treated asthmatics. They assessed asthma control in 4078 patients treated with ICSs attending general practice and showed that the pMDI was misused by 71% of patients; poor co-ordination was identified as the cause of this misuse in 47% of cases.\(^1\) The study highlighted the need to provide appropriate education to all patients, to evaluate patient inhaler technique and to reinforce the use of devices which alleviate co-ordination problems in pMDI misusers. Asthma was less stable among pMDI misusers than in good users (\(P<0.001\)), and among misusers, asthma was less stable in poor co-ordinators (Fig. 1).\(^1\) Common co-ordination problems encountered whilst using pMDIs include triggering the inhaler before inspiration or at the end of inspiration and concluding triggering whilst holding breath.\(^2,3\) Dry powder inhalers (DPIs) have many advantages over MDIs. They are breath-activated, thus alleviating co-ordination problems, are easy and convenient to use and are environmentally friendly.

When evaluating an inhalation device, it is important to consider patient compliance, drug deposition within the airways, and clinical efficacy. It is essential that inhalers are easy to use, as ease of use has implications for patient compliance. Additionally, an inhaler device should be chosen which maximises drug deposition in the lung. Pressurised MDIs typically deliver only 1/3 of the amount of drug to the lungs compared with the newer DPIs.\(^4,5\) However, with DPIs there is a direct relationship between the inspiratory flow rate generated by the patient and particle size distribution; only particles of a certain diameter can be deposited in the lungs. The aim of this article is to identify the key features of a DPI, which make it suitable for asthmatic patients of all ages and severity. The Novolizer\(^R\) as a new multidose DPI and the Turbuhaler\(^R\) as frequently used DPI are considered in particular. The relationship between inspiratory flow rate and particle size and how these parameters affect deposition of drug in the airways is assessed. Finally, clinical data examining the suitability of the Novolizer\(^R\) for use in children and comparing peak inspiratory flow rate (PIF) generated through the Novolizer\(^R\) and the Turbuhaler\(^R\) by adults with moderate-to-severe asthma or chronic obstructive pulmonary disease (COPD) is reviewed.

Factors affecting compliance

Feedback signals

The Novolizer\(^R\) has multiple feedback signals which reassure the patient that sufficient drug has been released from the device in order to deposit adequate therapeutic agent into the lungs. The feedback system ensures that the Novolizer\(^R\) is easy to use and to teach, it guides patients through the inhalation procedure. The success of the release of drug powder and correct inhalation is announced to the patient optically by a colour change in the display window. If the patient correctly inhales through the Novolizer\(^R\), the indicator switches from green to red. If the patient did not generate a sufficient inspiratory flow through the Novolizer\(^R\), the indicator colour remains green indicating that the device is still ready to inhale from. Correct inhalation is announced to the patient also acoustically in the form of a ‘click’, which further reassures the patients that they have inhaled correctly and that medication has been delivered. Finally, as the carrier
particles are lactose, a sweet taste in the mouth signals that powder has been successfully released from the inhaler and (in combination with the other feedback systems) further reassures the patient. The dose counter is also indirectly linked to correct inhalation, which might help to check the patient’s compliance easily.

Several other MDPIs such as the Turbuhaler® do not provide direct or indirect feedback mechanisms for the patient.

Trigger flow valve

Patients are often unsure whether or not they actually inhaled medication into their lungs. The Novolizer® reduces this uncertainty as it contains a novel flow trigger valve system. The flow trigger valve ensures that sufficient powder is released under the proper flow rate conditions (in the case of the Novolizer® this flow rate is from 35 to 50 l/min upwards) making the Novolizer® an excellent choice for patients with poor inhalation technique.

Drug deposition within the airways

Flow rate dependency of particle size distribution

With DPIs, particle size, respirable particle fraction and consequently drug deposition and distribution within the airways are critically dependent on inspiratory flow rate achieved by the patient. This is important as the fine particle fraction (FPF) of therapeutic agent is directly related to its clinical effect. Fig. 2 shows the emitted mass of 200µg budesonide powder for inhalation delivered by the Novolizer®, which does not increase markedly as the flow rate increased from 40 to 80 l/min.7 Even the respirable FPF is relatively independent of patients’ inspiratory flow profile.

However, with the Turbuhaler®, the particle size of the released powder is markedly affected by patients’ flow profile8 (Fig. 3). If a patient inhales maximally through the Turbuhaler® at the beginning of the inhalation manoeuvre most of the emitted particles are between 3 and 6µm in diameter and so would be deposited within the lungs. If, however, the patient inhaled slowly at first and then gradually increased the force of their inhalation as they progressed, then the size of emitted particles shifts dramatically to the right. In this scenario most of the particles are over 100µm in diameter which are far too large to inspire and so would be deposited in the mouth and oropharynx (Fig. 3).

As mentioned previously, with DPIs the in vivo lung deposition can be influenced by patients’ inspiratory flow rate.9,10 Using a well-validated gamma scintigraphic technique, Newman and colleagues11 evaluated the delivery of budesonide (200µg single radiolabelled dose) from the Novolizer® at different flow rates and compared this with delivery from the Turbuhaler® used at its optimal flow rate. The performance and FPF of budesonide 200µg formulation (nominal mass = 10.9 mg) flow rate corresp. to a pressure drop of 4 kPa.

![Figure 2](image-url) Emission performance and FPF of 200µg budesonide powder for inhalation using the Novolizer®. Reprinted with permission from Fyrnys et al.7

![Figure 3](image-url) Particle spectrum of the Turbuhaler® achieved by different inspiratory flow profiles. Reprinted with permission from Everard et al.8
flow rate. The Novolizer® was examined at 60 and 90 l/min but also at a low flow rate (45 l/min) to show its performance even at low flow conditions. The study consisted of 13 healthy volunteers and had a randomised cross-over design. Results showed that the Novolizer® achieved at least as much deposition of budesonide in the lungs as the Turbuhaler® when used at similar inspiratory flow rates. However at higher flow rates, the Novolizer® delivered significantly more drug to the lung and resulted in significantly less deposition in the mouth and oropharynx compared to the Turbuhaler® most likely due to its lower intrinsic resistance11 (Fig. 4). The pattern of regional lung deposition in the lungs was independent of flow rate, with good penetration to the lung periphery at all flow rates tested. This is an important result as the deposition of asthma drugs in the lungs is closely linked to their subsequent clinical effects.12,13

Clinical data on inspiratory flow rate

Comparison of Novolizer® and Turbuhaler®

To optimize inhaled treatment, the internal resistance of DPIs and sufficiently high inspiratory flow should be taken into account. Each inhaler has a unique intrinsic resistance, with values varying widely from inhaler to inhaler. The inspiratory flow rate which a patient can generate through a DPI is inversely proportional to the intrinsic resistance of the device (i.e. patients can achieve high inspiratory flow rates with a low resistance device). Previous studies with different DPIs have demonstrated that within certain patient groups, especially those patients with a high degree of airflow obstruction or in children, not all patients are able to reach the optimal inspiratory flow rate required to deposit drug in the lungs.14,15 Therefore, it is important to identify those patients who can use a given device. By using special meters (e.g. In-Check Dial®) which mimic the internal resistance of various DPIs or by combining a standard spirometer with the DPI it is possible to determine the individual peak inspiratory flow rate (PIFR) achieved by a patient during inhalation through a selected device.

Emeryk et al. showed that in 64 children aged 6–12 yr with different degree of airway obstruction only 75% attained PIFR adequate for the Turbuhaler® (> 60 l/min) and with regard to the Aerolizer® only 30% of patients achieved optimum PIFR (> 120 l/min).14 A study in 74 elderly COPD patients using the Turbuhaler® showed that 19% of these patients generated a PIF of < 30 l/min, 42% generated between 30 and 40 l/min and 31% generated between 40 and 60 l/min.15 Only 8% of patients (n = 6) were capable of generating a PIF rate > 60 l/min which is the optimal flow rate for the Turbuhaler®. By contrast based on these PIF values, the Novolizer® would be suitable for use by 90% of these patients. The low-to-medium intrinsic resistance of the Novolizer® lends itself to the treatment of these patients with low PIF or severe airflow obstruction. In a randomised, open-label study Leupold and colleagues16 assessed whether children aged 4–11 years with stable bronchial asthma could generate sufficient PIF through the Novolizer®. Results showed that all children, even those aged 4–5 years, were capable of generating a PIF greater than the trigger threshold of the Novolizer® (Fig. 4). The mean PIF (maximum of three attempts) through the Novolizer® generated by these asthmatic children was 76 l/min which is significantly above the technical PIF necessary to overcome the trigger threshold. The PIF was age dependent with the older children capable of generating the higher PIF values with an upper limit of about 86 l/min in the age class 8–9 years (Fig. 5).

In a similar study, von Berg and colleagues17 investigated the PIF which could be generated through the Novolizer® (PIF-N) compared to the

Figure 4 Scintigraphic images obtained using the Novolizer® at targeted inhaled flow rates of: (a) 90 l/min; (b) 60 l/min; (c) 45 l/min; and (d) the Turbuhaler® at a targeted inhaled flow rate of 60 l/min. Reprinted with permission from Newman et al.11

Successful inhaler use
Turbuhaler® (PIF-T) by children aged 6–11 years with stable asthma. The study comprised 48 children and had an open, randomised, multicentre design. No treatment was administered. Results confirmed the usability of the Novolizer® for children aged >6 years and demonstrated that the PIF generated through the Novolizer® was significantly ($P<0.0001$) higher than through the Turbuhaler® in all age groups assessed (Fig. 6). In addition, all patients were able to overcome the trigger threshold of the Novolizer®. Both PIF-N and PIF-T were age-dependent up to 8–9 years. These results confirm the usability of the Novolizer® for children of 6 years of age and older and demonstrate that significantly higher PIFs can be achieved through the Novolizer® compared to the Turbuhaler®. The authors concluded that together with the integrated visual and acoustic feedback for correct inhalation, the Novolizer® offers several useful advantages in the treatment of asthma in paediatric patients.

Preliminary results from another study which assessed PIFs generated through the Novolizer® and Turbuhaler® in adults with moderate-to-severe asthma ($n = 49$) showed that patients were able to generate a significantly ($P<0.0001$) higher PIF through the Novolizer® (103±28 l/min) compared to the Turbuhaler® (73±17 l/min) (Richter et al.; data on file). Detailed data are given in Table 1. As with the paediatric patients, all adults included in the study were able to reach the trigger inspiratory flow threshold required to operate the Novolizer®.

Beside severe airflow obstruction in asthmatic patients, MDPIs have to be evaluated as well in other diseases with impaired lung function and consequently reduced inspiratory flow rates. A study in COPD patients ($n = 46$) produced similar results (Table 2) (Richter et al.; data on file). The PIF-N observed in patients with all stages of COPD assessed (stages IIA–III) were significantly higher than PIF-T ($P<0.0001$; mean difference 31 l/min). The best predictor of PIF-N or PIF-T was found to be PIF at baseline, not forced expiratory volume in 1s (FEV$_1$) or GOLD stage. Therefore, when deciding on which inhaler to prescribe a COPD patient or a patient with severe asthma a measure of inspiratory flow rate rather than FEV$_1$ or peak expiratory flow rate (PEF) is more relevant.

**Conclusion**

Considering key parameters of DPI systems including compliance, drug deposition and achieved inspiratory flow rates is essential for selection of a device for different patient groups or an individual patient. The Novolizer® is a multidose refillable DPI. It has multiple feedback mechanisms, a unique trigger flow valve system and low-to-medium intrinsic resistance. Particle size is relatively independent of flow profile. This means that the Novolizer® forgives poor patient technique, improves deposition of sufficient drug into the

**Table 1**

<table>
<thead>
<tr>
<th>N (ITT)</th>
<th>PIF-T (l/min)</th>
<th>PIF-N (l/min)</th>
<th>PIF-N/T-ratio</th>
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<tr>
<td>49</td>
<td>103±28</td>
<td>73±17</td>
<td>1.40</td>
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</table>

ITT: intent-to-treat; PIF-N: peak inspiratory flow rate achieved through the Novolizer®; PIF-T: peak inspiratory flow rate achieved through the Turbuhaler®.
lungs, reassures the patient that medication has been taken and may facilitate improved patient compliance. The low-to-medium intrinsic resistance and the integrated visual and acoustic feedback mechanisms make the Novolizer® suitable for children, elderly patients and those patients with impaired inspiratory flow rates due to airway obstruction in asthma or COPD. Data from clinical studies show higher inspiratory flow rates for the Novolizer® in all patient groups as compared to the Turbuhaler®.

References

### Table 2

<table>
<thead>
<tr>
<th>COPD stage</th>
<th>N (ITT)</th>
<th>PIF-N (l/min)</th>
<th>PIF-T (l/min)</th>
<th>PIF-N/T ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
<td>25</td>
<td>95±22</td>
<td>64±20</td>
<td>1.38</td>
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<tr>
<td>IIb</td>
<td>18</td>
<td>97±15</td>
<td>65±15</td>
<td>1.37</td>
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<tr>
<td>III</td>
<td>3</td>
<td>81±21</td>
<td>60±15</td>
<td>1.36</td>
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<tr>
<td>All</td>
<td>46</td>
<td>95±19</td>
<td>64±18</td>
<td>1.37</td>
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</table>

COPD: chronic obstructive pulmonary disease; ITT: intent-to-treat; PIF-N: peak inspiratory flow rate achieved through the Novolizer®; PIF-T: peak inspiratory flow rate achieved through the Turbuhaler®.