Guidelines versus clinical practice—which therapy and which device?

J. Christian Virchow*

Department of Pneumology, University Medical Clinic, 18057 Rostock, Germany

Summary  Inhalation therapy delivers therapeutic agents directly into the lungs of patients with asthma, and is likely to remain the route of delivery of choice for the foreseeable future. The majority of patients with asthma suffer from mild intermittent to mild persistent disease for which regular low dose inhaled corticosteroids and on demand short-acting β2-agonists have been recommended. These highly effective anti-asthma medications are readily available, and so in the future improvement in asthma therapy will most likely derive from improvements in inhaler technology. Dry powder inhalers (DPIs) have many advantages compared to chlorofluorocarbon pressurised metered dose inhalers. Most notably, with DPIs patients no longer need to co-ordinate activation of the inhaler with inspiration. The Novolizer® (VIATRIS, Germany) which is one of the latest developments in DPI technology offers a number of features required to increase the safety and efficacy of inhaled therapy. It is the first DPI to include an inspiratory trigger threshold, which helps to prevent sub-optimal dose administration. Repeated activation without inhalation is mechanically inhibited by an overdose prevention mechanism. In conclusion, there is good evidence that technically refined DPIs are more likely to advance inhaled anti-asthmatic therapy than newly developed inhaled drugs. This is important when inhalation therapy is considered not only for asthma but also for chronic obstructive pulmonary disease.

Introduction

Inhalation therapy is the preferred route of administration of anti-asthmatic drugs to the airways due to its rapid, efficient and safe delivery. Adverse events of inhaled medication are markedly reduced due to the low systemic availability of inhaled medication compared with systemic doses of similar anti-asthmatic potency. Until recently most of these drugs were administered as aerosols...
from chlorofluorocarbon (CFC) pressurised metered dose inhalers (pMDIs). Since CFCs have been banned as propellants in order to protect the atmosphere’s ozone layer, hydrofluoroalkane (HFA) propellant pMDIs have been introduced. Dry powder inhalers (DPIs) which are propellant-free and accepted for inhaled asthma therapy have become an increasingly popular alternative to pMDIs as they are environmentally friendly, easy to use and deliver more drug to the lungs. Common to all DPIs is the fact that desagglomeration of the powdered medication is caused by the inspiratory flow generated by patients which makes drug delivery inspiratory flow-dependent. DPIs offer a number of advantages to conventional CFC-MDIs without necessarily increasing costs. One of their main advantages is that inhaler activation and inhalation of the aerosol requires no coordination by the patient. This article reviews the factors which influence clinicians’ decisions regarding which therapy and which device to prescribe to patients, to summarise the characteristics of the Novolizer® (VIATRIS, Germany) a recently introduced device with a number of unique features to deliver medication to the lungs; and to review clinical trial data with the Novolizer® in patients with asthma and chronic obstructive pulmonary disease (COPD).

### Which therapy?

The Global Initiative for Asthma (GINA) guidelines advocates a stepwise approach to both classify asthma severity and guide treatment. As asthma severity increases, the dose of inhaled corticosteroids (ICSs) is stepped up and other classes of drugs are added, particularly long-acting β₂-agonists (LABAs). Other agents recommended for addition to ICS therapy include sustained release theophylline, leukotriene modifiers, long-acting oral β-agonists and oral corticosteroids, depending on availability of these drugs and the severity of asthma. Once control of asthma has been achieved and maintained for at least three months, a gradual reduction of the maintenance therapy is recommended to identify the minimum therapy required to maintain control.

DPIs can deliver short- and long-acting β-agonists, corticosteroids, anticholinergics and also combinations of LABAs and ICSs. However, at present it is unclear whether the use of this combination (although effective in relieving and preventing asthmatic airflow obstruction irrespective of its severity) is indeed necessary and indicated in mild asthma. Current guidelines recommend their use only in moderate and severe asthma. Recent studies have shown better control of asthma compared with inhaled corticosteroids alone only for patients with stage III asthma (FEV₁ < 80% of predicted). Combination treatment has a potential disadvantage because it does not allow dose variation of one component if this is needed according to the actual stage of severity. In contrast to clinical experience recent animal studies suggest that regular combination therapy might enhance features of airway remodelling such as collagen and fibronectin deposition in the airways.

### Which device?

The GINA guidelines recommend DPIs or breath-activated MDIs for children older than 6 years. These guidelines also stipulate that inhalers should be portable and simple to operate (particularly important for children), should not require external power supplies, require minimal co-operation and coordination and have minimal maintenance requirements. Interestingly only the British Thoracic Society guidelines mention one of the most important aspects of successful therapy: patients’ preferences and abilities to correctly use the device should also be considered when deciding on a specific inhaler.

PMDIs have been used to deliver asthma medication to the lungs for almost half a century. However, they have many disadvantages both in terms of effectiveness and usability. They are inefficient, typically delivering only about 1/3 of the emitted dose to the lungs and less than half of the emitted dose to the peripheral airways compared to DPIs. They also require good coordination of inhaler activation and inspiration to ensure correct inhalation and deposition of drug in the bronchial tree. Misuse of pMDIs has been shown to be the rule rather than the exception, mainly due to poor coordination, and this correlates with poorer asthma control in asthmatic patients treated with ICS. Use of pMDIs without a spacer can lead to the deposition of a large percentage of the therapeutic agent in the mouth and pharynx. This can be overcome in part with large volume spacers, which are cumbersome and bulky and can negatively affect patients’ compliance. In addition, there are also significant differences in dose output from different combinations of pMDIs and spacers. Finally, for optimal dose delivery PMDs require an optimal inspiratory flow, a full inspiration from functional residual capacity and a breath hold of at least 6 s. Correct use of MDIs thus requires intensive training by the physician and regular technique re-testing may also be necessary.
Furthermore, pMDIs have neither inhalation control mechanisms nor dose counters. Although HFAs have reduced the velocity of the aerosol emitted compared to CFC-aerosols, these pMDIs can still cause irritation to the back of the throat stopping patients from inhaling (cold freon effect) which, occasionally can also cause bronchoconstriction.21

What criteria should be employed when choosing a device for inhalation therapy? The device itself should deliver an accurate and reproducible dose throughout its lifetime to ensure safe drug delivery. It should be easy and convenient to use, easy to teach, deliver a range of molecules, have an accurate dose counter, give patient feedback that they have used the device correctly, be conveniently carried, robust, visually appealing and CFC-free. The ability to deliver a range of drugs is clinically a very important feature since the likelihood for errors increases when more than one inhaler (for different drugs) is used.22 The pulmonary function of the patient and their ability to correctly use the inhaler device should also be considered. For example, patients with more severe airflow obstruction, which might interfere with a co-ordinated inspiration of a sufficient inspiratory flow, should preferably be treated with either a nebuliser, low intrinsic resistance DPI or a pMDI. Patients who experience difficulty co-ordinating inhaler activation with inhalation might profit from a DPI where coordination is not required. Poor coordination using pMDIs is a common problem,15,16 but can be overcome by the use of a spacer device. However, patients often complain that these are bulky and cumbersome to carry which can affect compliance, especially when travelling. From a clinical viewpoint it is worth mentioning that prescribing high quality drugs even in the most patient-friendly devices can be ineffective unless patients comply with this treatment. Interestingly, it has been shown that even patients who experience more than 10 exacerbations per year can have a relatively low compliance rate.23 Thus any inhaler device which can improve patient compliance should be regarded as a further advance in treatment.

A wide variety of DPI systems have been introduced to the market. Although each of these devices have unique advantages, unfortunately they also have many inherent limitations. Most DPIs currently on the market provide easy and effective drug delivery. DPIs are all breath-activated, precluding the need for the patient to co-ordinate inhaler activation with inhalation. They do not contain environmentally unfriendly propellants and do not produce unpleasant sensations during inhalation. The ideal DPI should also provide feedback to the patient and indicate a successful inhalation (e.g. from optical, acoustic and/or sensory feedback signals).

The Novolizer®

Inhaler characteristics

The Novolizer® is a multidose, breath-activated, refillable DPI with several innovative features offering unique inhalation control and patient feedback. It is equipped with an inhalation control system that helps to ensure the deposition of a particular drug into the bronchial tree. Patients receive an array of feedback signals indicating correct and successful inhalation. This is achieved by: (a) a colour change in the display window which confirms that powder has been released using optimal inspiratory flow; (b) a correct inhalation is confirmed acoustically by a 'click' giving the patient additional feedback on successful actuation; (c) as the carrier particles are lactose, a sweet taste on the tongue confirms (in combination with the other feedback features) that drug has been effectively released; and (d) the Novolizer® also contains a dose counter which resets only after a correct inhalation, and allows the respective caregiver to check compliance.

The most important advantage of the Novolizer®, however, is the flow trigger valve system. The device is activated and releases drug only if a certain inspiratory flow necessary for drug deposition in the lower airways is reached. This helps to ensure sufficient lung deposition as long as an inspiratory flow in the range of 35–50 L/min or higher is reached.24 Otherwise, the patient does not receive any of the feedback mechanisms mentioned above. This mechanism not only ensures efficient delivery of the drug to the lower airways but also overcomes poor patient inhalation technique. The quality of the aerosol delivered by the Novolizer® depends on a helix or cyclone in the mouthpiece which is needed for desagglomeration of the aerosol particles and enables maximum utilisation of the inspiratory flow energy. This improves flow of drug particles into the bronchial tree and reduces deposition losses. In addition, each dose from the Novolizer is almost entirely emptied from the device ensuring consistency of dose. Its low-to-medium airflow resistance also facilitates patients’ inhalation,25 since high resistance DPIs have been shown to release less medication in response to lower inspiratory flows26 and may increase the load on fatigued respiratory muscles. The device has been shown to
be reliable and durable during ‘real life’ conditions and neither the emitted dose of the drug nor the handling of the device is influenced by temperature or humidity.\textsuperscript{25}

Clinical studies

The efficacy, safety and tolerability of the Novolizer\textsuperscript{R} have been compared with older inhalation devices. The effects of salbutamol inhaled from a Sultanol\textsuperscript{R} pMDI or from a Novolizer have been compared in patients with COPD\textsuperscript{27} and the effects of budesonide administered from a Pulmicort Turbuhaler\textsuperscript{R} or via the Novolizer have been compared in patients with asthma.\textsuperscript{27,28}

In a randomised, controlled multicentre study, 257 patients with moderate-to-severe COPD including patients with asthma were treated with salbutamol (100 \( \mu \)g/actuation) using either the Novolizer\textsuperscript{R} or a pMDI.\textsuperscript{27} Patients attended a two week run-in phase where they received open-label treatment with a standard salbutamol pMDI (100 \( \mu \)g/puff). Then a double-dummy single use of salbutamol DPI and MDI was followed by a test of lung function over 1 h (acute treatment). The study then continued with an open label, randomised long term treatment phase with either the Novolizer\textsuperscript{R} or salbutamol MDI for a further 4 weeks. Results showed that the salbutamol Novolizer\textsuperscript{R} and pMDI were therapeutically equivalent in terms of improvement in lung function in these patients with COPD.\textsuperscript{27} After 4 weeks of treatment, both groups showed similar improvements in forced expiratory volume in 1 s (FEV\textsubscript{1}), peak expiratory flow (PEF) and symptom score. The maximum % increase in FEV\textsubscript{1}, following a single administration of salbutamol was 21.3% in the Novolizer\textsuperscript{R} group compared with 19.7% in the pMDI group. However, the response to treatment in terms of global assessment of efficacy was rated as very good/good by more patients in the Novolizer\textsuperscript{R} group (78%) compared to the pMDI group (69%). Furthermore, of those patients who had previously used a pMDI (92%), 78% stated that they would rather use the Novolizer\textsuperscript{R} in the future and 59% expressed a preference for the Novolizer\textsuperscript{R}. Of those patients who had previously used a DPI, 87% favoured the Novolizer\textsuperscript{R} to their previous DPI.\textsuperscript{27}

In another randomised, controlled, open-label, multicentre study, 315 patients with mild-to-moderate bronchial asthma were treated for 12 weeks with budesonide (200 \( \mu \)g bd) delivered by either the Novolizer\textsuperscript{R} or the Turbuhaler\textsuperscript{R}.\textsuperscript{27,28} The primary efficacy parameter was FEV\textsubscript{1} at the end of the treatment period. Secondary efficacy variables included other pulmonary function tests (e.g. PEF), bronchial hyperresponsiveness to histamine, rescue \( \beta_2 \)-agonist use, assessment of asthma symptoms and global assessment of efficacy. The primary analysis of FEV\textsubscript{1} which was the study’s end-point showed equivalent efficacy between the Novolizer\textsuperscript{R} and the Turbuhaler\textsuperscript{R} (Novolizer\textsuperscript{R}: 2.71L ± X.XL; Turbuhaler\textsuperscript{R}: 2.74L ± X.XL; Diff: −0.03; 95% CI: −0.19–0.13; \( P<0.001 \)).\textsuperscript{27,28} All other parameters in the pulmonary function tests as well as asthma symptoms, nocturnal awakenings, PEF recordings (Fig. 1) and rescue medication use (Fig. 2) showed no significant or clinically relevant differences between the two groups. Efficacy was considered by the investigator to be ‘very good’ or ‘good’ in the majority of patients in both groups (Novolizer\textsuperscript{R} 87%; Turbuhaler\textsuperscript{R} 79%). Both groups had a similarly low incidence of adverse events and paradoxical bronchospasm. Safety monitoring, which included vital signs, laboratory, ECG and ophthalmological findings revealed no evidence for clinically relevant effects attributable to the study. Furthermore, the 24 h urinary cortisol concentrations were similar in both groups. The majority of investigators assessed the tolerability

- Figure 1 Effect of 12 weeks treatment with budesonide (200 \( \mu \)g bd) delivered via the Novolizer\textsuperscript{R} or Turbuhaler\textsuperscript{R} on peak expiratory flow (PEF) in patients with mild-to-moderate asthma. Reprinted with permission from Chuchalin et al.\textsuperscript{28}
of the Novolizer® and Turbuhaler® as ‘good’ or ‘very good’. In summary these results show similar efficacy, safety and tolerability for the Novolizer® compared to either a pMDI or the Turbuhaler. Interestingly, in terms of patient preferences the Novolizer® was superior to either MDI or the DPI used in these studies.

Post marketing surveillance study

The objectives of the post-marketing surveillance study were to collect data on the efficacy, tolerability and acceptance of the Novopulmon® 200 Novolizer® in patients with asthma. The study comprised 3057 patients from 963 centres in Germany. The median duration of the monitoring period was 31 days and the median dose of budesonide was 400 μg/day. Results showed that following 4 weeks of treatment with the Novolizer®, median PEF increased from 5 to 6.3 L/s and FEV₁ increased from 2.25 to 2.7 L (Fig. 3). The severity of symptoms decreased accordingly during the course of this surveillance. The median total symptom score fell from 8 prior to initiation of therapy to 2 at the end of the observation period. The percentage of patients who had symptoms of cough, wheezing, diurnal dyspnea, nocturnal dyspnea and dyspnea on physical effort before and after treatment are summarised graphically in Fig. 4.

Conclusion

The choice of the device for inhalation is a prerequisite for a successful inhalation therapy. Patients’ pulmonary function and his/her ability to correctly use a device have to be considered as well as the efficiency of the device. Requirements for an
ideal inhaler include delivery of an accurate and consistent dose, easy handling by the patient and feedback mechanisms which indicate successful inhalation. Since the budesonide Novolizer has been shown to be clinically as effective as a budesonide Turbuhaler in patients with asthma and when filled with salbutamol to be as good as a standard pMDI in patients with COPD, this new inhalation device with its several feedback feature offers a patient-friendly alternative to standard inhalation therapy. This is highlighted by the observation that more patients preferred the Novolizer compared to their previous MDIs or DPI. In accordance with the GINA guidelines on asthma therapy the Novolizer can deliver an ICS (i.e. budesonide) for maintenance therapy, as well as a short-acting $\beta_2$-agonist (i.e. salbutamol) for as needed treatment of acute episodes of bronchospasm. In addition the Novolizer can be filled with a LABA (i.e. formoterol) to treat nocturnal symptoms or more severe asthma in combination with an ICS. The Novolizer’s technical features can improve efficacy, safety and compliance. In conclusion, the Novolizer is a DPI which meets most of the criteria required for an ideal inhaler device and can deliver a range of drugs recommended by international management guidelines for the treatment of asthma and COPD.

References