How to achieve good compliance with inhaled asthma therapy

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Summary

Inability to use inhaler devices correctly is a major source of non-compliance in patients with asthma. The problem of coordinating dose release with inspiration seen with pressurised metered dose inhalers (pMDIs) is overcome by dry powder inhalers (DPIs), since they use inspiratory flow energy to carry the drug dose to the respiratory tract. The first DPIs were not popular because they were single dose devices and inconvenient to use. The introduction of multiple dose DPIs improved the image of the dry powder systems in the eyes of both the clinician and the patient. The continued development of DPIs has led to inhaler devices which include dose counters, are easy to use, are refillable and provide feedback to the patient on a correct inhalation. Criteria that may improve patient compliance with an inhaler include: correct use of the device by most patients; ease and convenience of device use; dose release even at low inspiratory flow rates; feedback of drug release which could instill confidence that the dose has been inhaled; cartridge refills and overall confidence in the device. The Novolizer® has all the desirable features listed above and is expected to improve compliance if prescribed for the large number of patients who cannot use the conventional pMDI or less efficient DPIs.

Introduction

There are numerous factors that influence patients’ compliance with drug therapy. In asthma, the problem is greatly increased since inhaled treatment is the rational mainstay of therapy. Compared to oral medication many patients find the inhaled route is unnatural and this problem is compounded by the fact that many inhalation devices are difficult to use even by the most compliant patients. The pressurised metered dose inhaler (pMDI) was first introduced into clinical practice in 1956 in the USA. It very quickly became popular with clinicians and remains the most commonly prescribed inhalation device today, even though its design has remained unchanged for many years and many patients find it difficult to use.1,2 Inability to
use inhaler devices correctly is a major source of patient non-compliance with therapy. At least 50% of adults and even more children cannot use pMDIs efficiently mainly because of the difficulty of coordinating dose release with inspiration. In this large proportion of the asthmatic population good compliance with treatment is therefore impossible irrespective of the individual patient’s desires.

This article will discuss the problems associated with pMDIs and dry powder inhalers (DPIs) currently on the market, as well as factors likely to improve patient compliance and examine how the many features of the Novolizer\(^\text{TM}\), a new multidose DPI produced by VIATRIS Germany, could improve patient compliance.

Natural history of inhaler devices

In 1956, almost 50 years ago, the pMDI was launched in the US and has remained essentially unchanged since then. However, it soon became apparent that many patients had difficulty using this device correctly, most notably coordinating device activation with inspiration proved problematic. Coordination difficulties resulted in deposition of a large proportion of drug in the mouth and oropharynx. Spacers were introduced in the 1970s and 1980s to eliminate this problem, but the bulky nature of spacers made them inconvenient to carry and so were not conducive to compliance with therapy. In an effort to preclude the need for patients to coordinate device activation with inhalation, the first successful breath-activated pMDI was launched in 1989 in the UK. These breath-activated inhalers were much easier for patients to use correctly. However, in 1995 the Montreal Protocol banned the use of chlorofluorocarbon (CFC) propellant gases in pMDIs in a bid to protect the ozone layer from further depletion. Ironically, pharmaceutical companies replaced CFCs with hydrofluorocarbons (HFAs) which are 2000 times more potent greenhouse gases than CFCs.

DPIs first appeared on the market in the late 1960s. The Spinhaler\(^\text{TM}\) (Fisons) was introduced in 1969 to deliver sodium cromoglycate as pMDIs were not suitable to deliver this drug in sufficient quantities. The Rotahaler\(^\text{TM}\) (GlaxoSmithKline) appeared in 1977 closely followed by the Diskhaler\(^\text{TM}\) (GlaxoSmithKline) in 1980, the first of the foil blister inhalers. The first multidose gravity feed DPI, the Turbuhaler\(^\text{TM}\) (Astra Zeneca), was introduced in the UK in 1988. The Diskus\(^\text{TM}\)/Accuhaler\(^\text{TM}\) (GlaxoSmithKline) was launched in 1994 and is a modification of the Diskhaler\(^\text{TM}\) system. Finally in 2001, the Novolizer\(^\text{TM}\) (VIATRIS, Germany) entered the market.

Disadvantages with pressurised metered dose inhalers

The main disadvantage with pMDIs is that patients cannot use them correctly. Patients frequently fail to continuously inhale slowly after activation of the inhaler and exhale fully before the inhalation. In addition, patients often activate the inhaler before inhalation or at the end of inhalation and conclude inhaler activation while breath-holding.

Gayrard and Orehek\(^4\) assessed pMDI use in a group of 115 asthmatics. Patients were divided into two groups. The first group received instruction on the correct use of their pMDI by a physician and the need for correct inhaler use was strongly emphasised. The second group received no instruction and used their inhaler according to manufacturers’ instructions. The inhalation technique was considered correct when (1) the puff release was coordinated with a deep inspiration and (2) when the inspiration was followed by a few seconds’ breath-holding. Seventy-two percent of patients who received no instruction were unable to use their pMDI correctly compared to 48% after physician training. A German study carried out in 207 patients revealed that almost half of these patients (47%) used their pMDI inadequately, women more frequently than men.\(^7\) Most frequent errors included an insufficient expiration before inhalation and a lack of coordination between inhaler activation and patient inhalation. A Spanish study in 1640 volunteers (746 patients, 466 nurses, 428 physicians) showed that a staggering 91% of patients were unable to use their pMDI correctly compared with 85% of nurses and 72% of physicians. Worryingly, general practitioners and paediatricians had the worst inhaler technique compared to chest physicians and allergists.\(^8\)

A series of studies by Crompton and colleagues investigating pMDI use during the period 1982–2000 produced similar results.\(^5,7,9,10\) Inhaler technique was assessed after patients read the inhaler package insert. Those patients who showed inadequate inhaler technique were instructed by trained personnel and then retested. Results are summarised in Table 1. In 1982, 80 patients (13%), out of an original 1173 out-patients attending hospital during a 3-month period, who had been able to use a pMDI efficiently in the part were found to have
developed a poor technique. Problems encountered operating the pMDI included difficulty coordinating aerosol release with inspiration (54% patients), stopping inhalation upon release of the aerosol (24% patients) and inspiriting through the nose whilst actuating the inhaler in the mouth (12% patients). In subsequent studies the percentage of patients who could correctly use a pMDI after reading the instruction pamphlet or after receiving instruction continued to fall (Table 1). By 2000, only 21% of patients were able to correctly use a pMDI after reading the package insert and only 52% of patients correctly used a pMDI after receiving instruction.

Previous ability to correctly use a pMDI was not indicative of correct use during subsequent testing. For example in a study carried out in 1976, 50 patients out of a total of 321 patients (14%) who had documented evidence of correct inhaler technique proved to have totally inefficient coordination of inspiration and inhaler activation. In a study carried out in 1982, 13% of patients already being treated with drugs by inhalation had a poor inhaler technique, even though most had received instruction on how to use a pressurised aerosol and were considered to be able to use one of these devices correctly. Furthermore, 12% (this should be of the 13% found to have an inefficient technique) of patients already being treated with inhalers actuated the aerosol on two or more occasions during one inspiration.

These observations suggest that the majority of asthmatic patients probably derive incomplete benefit from the use of pMDIs. Although training apparently results in a more efficient use of the canisters, training sessions must be repeated, and the results checked at regular intervals by a member of the medical staff. In patients who repeatedly fail to achieve a correct inhalation technique, the drug should be given using an alternative inhalation device. The improper use of pMDIs is not confined to patients. Both nurses and physicians have also been shown to use pMDIs incorrectly despite their increased awareness of the importance of a correct inhalation technique in the use of the pMDI. Substantial changes in educational efforts are clearly required and should be particularly addressed towards the general practitioner and asthma nurse who in turn teach patients how to use their inhaler device correctly.

Pressurised MDIs are clearly inefficient, user-unfriendly devices which require good coordination between inspiration and inhaler activation. Approximately 50% of adults are unable to use their pMDI correctly even when taught. Indeed, intensive training is required in the correct use of pMDIs and frequent retesting is also recommended. More than 10% of patients develop poor technique with continued use if checks are not made, and children have far more problems using the device than adults. Compared with new DPIs, pMDIs deposit approximately one-third of the drug into the lungs and deposition rates depend upon inhaler technique. Efficient use requires an optimal inspiratory flow and a breath-hold of at least 6 s. Used with a spacer device, bulkiness may reduce patient compliance; without a spacer device a high proportion of drug is deposited in the mouth and oropharynx. Finally, pMDIs contain no inhalation control mechanisms, have no dose counter, and contain environmentally unfriendly propellant gases (e.g. HFAs). On the plus side pMDIs are cheap and convenient. However, convenience is irrelevant if patients cannot use the device correctly. The consequence of not using a pMDI correctly is lack of clinical effect. Continually changing inhaler devices which deliver the same drug is not the answer, as patients not only lose confidence in the device but also in the drug and compliance with therapy becomes poor. Therefore, poor compliance with therapy can still occur even if the patient is switched to an inhaler that they can use. The lesson to be learned from this clinical experience is do not prescribe an inhaler unless you are absolutely certain that the patient can use it properly.

### Disadvantages with dry powder inhalers

The DPI is breath-activated and minimal coordination is required between actuation and inspiration. DPIs achieve higher pulmonary deposition than pMDIs and they are environmentally friendly as they do not contain propellant gases. There are many DPIs currently on the market. These devices

![Table 1](image-url)
are divided into single dose devices, multiple unit dose devices or multidose devices. Although DPIs, as a class of delivery device, offer both the patient and the physician many advantages over pMDIs, individually they do have some limitations of design, cost-effectiveness and/or user-friendliness.

**Spinhaler**

The Spinhaler® and Rotahaler® are single dose devices. Doses are individually loaded into gelatine capsules, each of which is loaded into the inhaler immediately before use. When using these devices there is no inhalation control system and the patient receives no feedback that the dose has been successfully released or that the patient has inhaled correctly. Additionally, a high inspiratory flow must be achieved to generate a fine particle fraction (FPF) suitable for drug deposition in the lungs. For each inhalation a new capsule needs to be inserted into the device which is inconvenient for the patient and does not allow for dose counting. Also, the inhalation process may have to be repeated until the capsule is empty which may give rise to high dose variability.

**Diskhaler**

The Diskhaler® (GlaxoSmithKline) was the prototype of the Diskus® and is still used to some degree in the UK, although it does have a complicated usage. It is an example of a multiple unit dose device as it contains a series of foil blisters on a disk. These disks have to be frequently changed and the device cleaned before refilling.

**Turbuhaler**

The Turbuhaler® is the most frequently prescribed DPI as it produces good deposition of drug in the lungs provided that a sufficient inspiratory flow has been achieved by the patients (i.e. 60 l/min). It is an example of a multidose reservoir device. However, many features of the Turbuhaler® generate uncertainty for both the physician and the patient. For example, the Turbuhaler® exhibits high dose variation, the particle size generated is dependent on patients’ inspiratory flow rate, it has lower drug deposition rates than the Novolizer® at optimal inspiratory flows and is not easy to use by virtue of its high intrinsic resistance. In fact, the resistance of the Turbuhaler® is approximately twice that of the Novolizer®. Using the Turbuhaler®, good deposition is only achieved when the patient achieves a sufficient inspiratory flow (i.e. > 60 l/min). At lower inspiratory flow rates, as may occur in young and elderly patients as well as those with severe airflow obstruction, inhalation through the Turbuhaler® is likely to result in high oral and low lung deposition. Indeed, patients may be able to easily generate 60 l/min one day but on another day, due to the variable nature of airflow limitation seen in asthma, may be unable to reach an inspiratory flow sufficient to operate the Turbuhaler® effectively. In addition, patients must inhale sharply through the Turbuhaler® at the beginning of the inhalation manoeuvre to ensure desagglomeration of drug particles and hence effective pulmonary drug deposition. Finally, there is no feedback to the patient that sufficient medication has been successfully delivered. The device is not refillable, there is no inhalation control mechanism, the dose counter is limited and the amount of drug released from the device might be reduced in conditions of high humidity.

### Pressurised MDIs vs DPIs

A study carried out by Crompton and colleagues assessed patients’ use of different inhaler devices, ascertained whether patient device preference was indicative of ease of use and whether current inhaler use had any influence on either technique or device preference. One hundred inhaler-naïve patients received instruction, in randomised order, in the use of several different inhaler devices (pMDI, Easi-Breath®, Authohaler®, Diskus®, Clic-khaler®, Turbuhaler®). After instruction patients were graded (using predetermined criteria) in their inhaler technique. Technique was best using the breath-actuated inhalers; the Easi-Breathe® and Autohaler®, with 91% of patients observed to have good technique following instruction (61% prior to instruction). The Turbuhaler® did not fare as well, with only 47% of patients being able to correctly use it after reading the package insert which rose to 90% following expert instruction. The pMDI fared worst of all, in last position with only 21% of patients showing good technique, despite being the most commonly prescribed device. Following instruction by an expert, only 52% of patients showed good inhaler technique with the pMDI. The majority of patients (55%) currently used the pMDI but the pMDI did not score highly for preference or achieve better grades than the other devices. This has important repercussions for drug delivery and hence disease control. There is no advantage to
be gained by prescribing a device that costs less but that the patient cannot use correctly. Prescribing a patient’s preferred device may increase cost but can improve efficiency and therefore be more cost-effective in the long-term. Using an inexpensive device (pMDI) when technique is good, or the patient’s preferred inhaler device when pMDI technique is poor is one way to optimise delivery and may even reduce cost.5

The Novolizer® may improve patient compliance

A large post-marketing surveillance study carried out in 3057 patients suffering from allergic, non-allergic or mixed bronchial asthma evaluated the efficacy, tolerability and acceptance of the Novolizer® (containing budesonide 200 µg).21 Most of the patients (54%) used a pMDI prior to the study, 21% of patients used a DPI but all were on inhaled corticosteroids prior to switching to the Novolizer®. Patients treated with budesonide delivered via the Novolizer® for 4 weeks showed a decrease in the severity of their symptoms. The median total symptom score fell from 8 before therapy to 2 after therapy. PEF also increased from 5 l/s prior to therapy to 6.3 l/s at the end of therapy, with a median individual increase of 11 l/s. FEV1 showed a similar improvement increasing from 2.25 l before therapy to 2.7 l after therapy (a median individual increase of 310 ml).21 This reduction in symptoms and improvement in lung function following treatment with the budesonide Novolizer® for 4 weeks may have been due to improved compliance with therapy.

Patients’ satisfaction in dealing with the control mechanisms (i.e. optical, acoustic, taste, dose counter, overdose prevention) of the Novolizer® was also assessed.21 Patients who already had used another inhalation system assessed the control mechanisms of the Novolizer® in comparison with their previous inhaler. Results of the study showed that the majority of patients were satisfied with the control mechanisms of the Novolizer® (Fig. 1). Ninety-seven percent of patients were satisfied with the optical control mechanism, 94% with the acoustic mechanism, 78% with the taste feedback, 92% with the dose counter and 81% with the overdose prevention system. This is an important result as patients who are satisfied with their inhalation device are more likely to be compliant with their treatment regimen. It follows that improved compliance should lead to improved asthma control.

Figure 1 Patient satisfaction with the control features of the Novolizer®. Reprinted with permission from Möller et al.21

Patients’ compliance and any improvement in compliance by the control mechanisms of the Novolizer® were evaluated by physicians and patients.21 Compliance was assessed by physicians to be good in 84% of the patients, satisfactory in 14% of patients and unsatisfactory in the remaining 2% of patients. An improvement in compliance by the control mechanisms of the Novolizer® was observed in 80% of the patients. Eighty-eight percent of patients felt that the optical feedback system improved their compliance, 81% thought the click noise improved their compliance but only 46% of patients thought the taste feedback improved their compliance. The vast majority of patients (91%) assessed the control mechanisms of the Novolizer® to be better or much better than those of a previously used inhaler (e.g. Diskus® or Turbuhaler®). These results suggest that the control mechanisms of the Novolizer® are well-accepted by patients and considered by physicians as an important contributor to improved patient compliance.

Conclusion

Factors important in patient compliance with therapy include correct use of inhaler device; ease and convenience of use; control of dose release; confidence that drug has been released and
inhaled; cartridge refills; and accuracy and consistency of dose release. The Novolizer® fulfils all these compliance criteria (Fig. 2). The Novolizer® is a convenient device and easy to use correctly. The portable nature of the device and multidose design make the Novolizer® convenient for patients to use. Ease of use as well as confidence that drug has been released is assured by the multiple feedback system which guides patients through the inhalation procedure in a step by step fashion. In addition, dose release is indicated by a trigger flow valve which helps to ensure that sufficient drug is released for optimal pulmonary deposition. The Novolizer® with its multiple feedback mechanisms and trigger flow valve system is a device which gives patients confidence that drug has been inhaled and deposited in sufficient quantities into their lungs. The Novolizer® is a refillable device which makes it an environmentally friendly and cost-effective option. Cartridge change is simply a matter of opening the inhaler, removing the old cartridge and replacing it with a new one. Drug release from the Novolizer® has been shown to be consistent under ‘real life’ conditions; the emitted mass and FPF of drug released from the device is relatively independent of patients’ inspiratory flow profile and unaffected by conditions of high temperature and humidity.22 Finally, patients who have used the Novolizer® express a preference for it and are satisfied with the control features of the device. In conclusion, the Novolizer® has many features which should improve patient compliance, and improved patient compliance should lead to better control of asthma.

References


Figure 2: Novel features of the Novolizer® which may improve patient compliance with therapy.