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REVIEW

Importance of inhaler devices in the management of airway disease

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Summary
The delivery of drugs by inhalation is an integral component of asthma and chronic obstructive pulmonary disease (COPD) management. However, even with effective inhaled pharmacological therapies, asthma, particularly, remains poorly controlled around the world. The reasons for this are manifold, but limitations of treatment guidelines in terms of content, implementation and relevance to everyday clinical life, including insufficient patient education, access to health care and cost of medication as well as poor inhaler technique are likely to contribute. Considering that inhalation therapy is a cornerstone in asthma and COPD management, little advice is provided in the guidelines regarding inhaler selection. The pressurised metered dose inhaler (pMDI) is still the most frequently prescribed device worldwide, but even after repeated tuition many patients fail to use it correctly. In addition, the correct technique can be lost over time. Although several improvements in pMDIs such as a change in the propellant and actuation have resulted in improvements in lung deposition, many dry powder inhalers (DPIs) are easier to use. However, these devices also have limitations such as dependency of drug particle size on flow rate and loss of the metered dose if the patient exhales through the device before

Abbreviations: CFC, chlorofluorocarbon; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FDA, Food and Drug Administration; HFA, hydrofluoroalkane; ICS, inhaled corticosteroids; FEV_1, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma; LABA, long-acting β_2-agonist; pMDI, pressurised metered dose inhaler

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inhaling. Improvements in using inhalation devices more efficiently, in inhaler design for supporting patient compliance, and advances in inhaler technology to assure drug delivery to the lungs, have the potential to improve asthma and COPD management and control. New and advanced devices are considered being helpful to minimise the most important problems patients have with current DPIs.

Contents

Introduction

Inhalation is the preferred route of delivery for anti-asthma and chronic obstructive pulmonary disease (COPD) drugs. As therapeutic agents are delivered directly to the lungs, the inhaled route offers a more rapid onset of action, allows smaller doses to be used and has a better efficacy to safety ratio compared to systemic therapy. Long-acting β_2-agonists (LABAs) and inhaled corticosteroids (ICSs) have become the pharmacological mainstay of management programmes, treating the symptoms of disease and the underlying inflammatory processes, respectively. Pharmacotherapy has advanced to such a degree that the goals of treatment, as outlined by the international treatment guidelines Global Initiative for asthma (GINA), expect asthma sufferers to be managed so that they can live normal lives with little or no symptoms, have no exacerbations, minimal need for reliever medication, normal lung function and no side effects.[1]

However, the current level of asthma control worldwide falls short of these goals for long-term management.[1] Despite the availability of effective therapies, asthma remains an illness that is insufficiently controlled.[2–4] Many patients with typical symptoms of asthma complain of wheezing, chest tightness, cough, breathlessness, asthma-related sleep disturbance and require unscheduled urgent care visits and emergency hospital admission due to asthma exacerbations.[2–4] In Eastern Europe and particularly in the Asiatic-Pacific region, hospitalisation and emergency admission rates remain the highest[4] (Figure 1). Even patients who feel well still complain of symptoms providing evidence that they under-estimate their own symptoms.[2] Asthmatic patients may also not follow GINA recommendations for medication use,[3] highlighted by the fact that only 26% and 9% of severe-persistent patients in Western Europe and Japan, respectively, used anti-inflammatory preventive medication.[4] Thus, asthma control remains a public health problem with variation not only among individuals but also across the socioeconomic spectrum. Patient education, access to health care and the cost of medications are likely to influence treatment results. Not all patients achieve reasonable control with the currently available medication, but there is little evidence to suggest that new drugs which are currently under development will put the disease in complete remission in the majority of patients.

From clinical practice as well as from observational studies, however, it is evident that a poor pressurised metered dose inhaler (pMDI) technique leads to poor treatment responses.[5–7] Any improvement in inhalation therapy therefore has the potential to improve outcomes of asthma therapy without introducing costly new treatment modalities. This review will, therefore, assess problems that can lead to poor inhaler techniques, which could contribute to poor asthma control. It will also summarise the many problems facing patients when using a pMDI, outline the generic advantages dry powder inhalers (DPIs) have over pMDIs and discuss individual limitations of DPIs currently on the market. In particular, the reliance of DPIs on inspiratory effort, the relationship between inspiratory effort and drug particle size, the significance of particle size and inspiratory speed on clinical effect and the theory that ideal particle size depends on drug class are discussed. Characteristic of an ideal inhaler device and what criteria are important for clinicians to know when selecting devices for individual patients are considered. Finally, the review shows the opportunity for improved asthma control when using advanced inhaler devices.

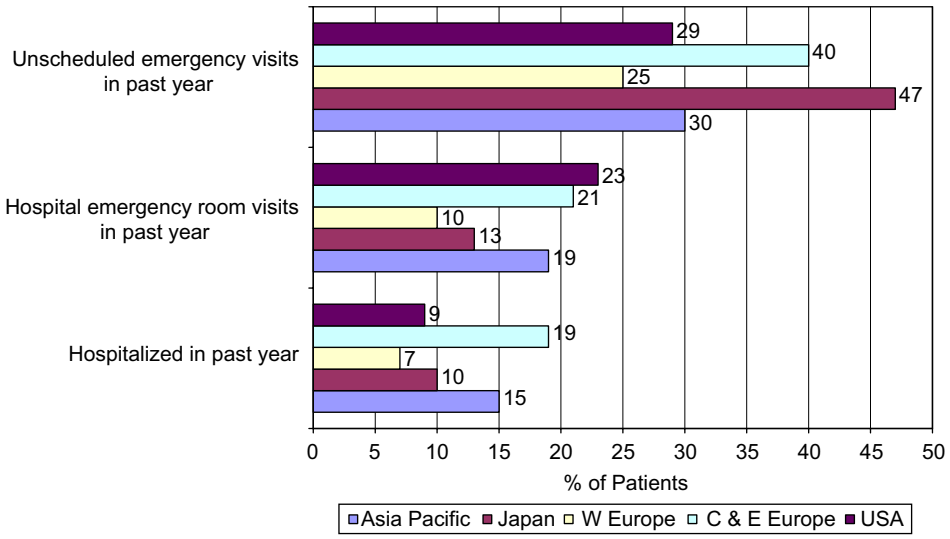

Figure 1 Rates of clinic admissions and emergency admissions due to uncontrollable asthma exacerbations are unacceptably high worldwide. Reprinted with permission from Ref. 2.

History of inhaled therapy

Inhaled therapy, which was developed within the last 50 years, is, and will remain for the near future, the cornerstone of asthma and COPD management. The first reports about the effectiveness of inhaled therapy came from as early as the beginning of the 20th century.[8–10] However, this therapy did not find widespread use until the middle of the 20th century after the introduction of the first propellant gas dosing aerosols in the form of pMDIs. Unfortunately, controversy surrounding the long-term use of regular β_2-agonist therapy emerged following epidemics of asthma deaths in the UK and New Zealand in the late 1960s and late 1970s, which were linked to the prescribing of high-dose isoprenaline and fenoterol, respectively.[11–14] Understandably, this brought the safety of inhalation therapy into question.[63] It was only after the introduction of selective β_2-mimetics and especially the introduction of ICSs that topical treatment became the therapy of choice for bronchial asthma and COPD.

However, the controversy regarding β_2-agonists resurfaced with the introduction into the market place of LABAs. Studies reported a higher risk of mortality under LABA therapy,[15–20] and the Food and Drug Administration (FDA) requested a black box warning for these drugs. Additional data suggest that ICSs must be dosed sufficiently high to guarantee effective suppression of the underlying inflammatory processes.[1] Monotherapy with LABAs should be avoided.[1]

Several new technologies involving liquid nebulisation have been developed for delivery of inhaled drugs, albeit for conditions other than asthma. Their clinical value is currently being established.

The key question: why is asthma so poorly controlled?

There are many reasons why asthma remains poorly controlled including underestimation of disease severity, delay in diagnosis, undertreatment (e.g. delay in starting ICS therapy), poor compliance with therapy, wrong inhaler choice and inhalation technique, insufficient instructions as well as ineffective guidelines. Failure to achieve asthma control may be due to a discrepancy between individual perceptions and the official definition of asthma control.[21] This discrepancy suggests a communication gap between health care providers and families, resulting in worse asthma control than previously anticipated.[2,3,21]

Limitations of treatment guidelines

Both national and international treatment guidelines suffer from many inherent limitations, which diminish their relevance in everyday practice.[22] The treatment guidelines may not take account of individual differences in response to treatment, neither can they take account of the availability and cost of pharmacological treatments worldwide. The evidence upon which they base their recommendations comes from randomised controlled studies with strict inclusion/exclusion criteria rather than from real life data,[22] and sometimes recommendations are consensus- and not evidence-based.

Treatment guidelines do not provide adequate recommendations on inhaler choice.[1,23] The guidelines do state that inhalers should be portable and simple to operate (particularly important for children), should not require an external power source, require minimal cooperation and coordination and have minimal maintenance requirements.[1] The British Thoracic Society guidelines also include patients' preferences and the ability to correctly use the device as issues to consider when choosing an inhaler.[23] Surprisingly, despite the well-documented problems with pMDI devices, GINA recommends pMDIs for children <4 years with a spacer and face mask, for those aged 4–6 years with a spacer and mouthpiece and for those >6 years with a spacer.[1]

Poor inhaler technique

Inadequate inhaler instruction and poor inhaler technique are another major cause of poor disease control, influencing

as they do the amount of drug that reaches the lung and compliance with therapy. Consequences of poor pMDI technique include a decrease in pulmonary deposition,[7] with a concomitant reduction in bronchodilator effect.[6,7] Whereas the mechanisms of action, the effectiveness and the significance of ICS as well as short- and long-acting β_2-agonists in the management of asthma and COPD are well-established, the importance of the mode of delivery of these agents, namely inhaler devices, is still disregarded, despite being mandatory components of asthma management.[1,22] This is a regrettable situation since inhaled drugs are the most effective therapy available for asthma and COPD, improvements in inhaler technology and design in combination with improvement in both physician and patient education seems to be the way forward in improving asthma management and control. In other words, an old but well-known drug in a new, more reliable inhaler is probably more useful than a new drug in an old (flawed) inhaler.[24]

The pMDI is still the most frequently prescribed inhaler device worldwide despite the fact that most patients cannot use it correctly.[25–31] This is because pMDIs require good coordination of patient inspiration and inhaler activation to ensure correct inhalation and deposition of drug in the lung.[25] Patients frequently fail to continuously inhale slowly after activation of the inhaler and exhale fully before the inhalation.[32,64] In addition, patients often activate the inhaler before inhalation or at the end of inhalation and conclude inhaler activation while breath-holding.[25,32] Several improvements in pMDIs such as a change in the propellant and actuation/coordination, however, have resulted in improvements in lung deposition.

A study of pMDI use in a group of 115 asthmatics showed that 72% of patients who received no instruction were unable to use their pMDI correctly compared with 48% after physician training. Another study carried out in 207 patients revealed that almost half of these patients (47%) used their pMDI inadequately, women more frequently than men.[31] Similarly, a Spanish study in patients, nurses and physicians ($n = 1640$)[30] showed that 91% of patients were unable to use their pMDI correctly compared with 85% and 72% of nurses and physicians, respectively.

A series of studies performed by Crompton and colleagues between 1982 and 2000 confirmed these findings.[25,26,29] 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 re-tested. In 1982, 54% of inhaler-naïve outpatients were unable to use a pMDI efficiently after reading an instruction pamphlet or having the correct use of a pMDI demonstrated to them.[25] Common problems experienced by patients using the pMDI included difficulty coordinating aerosol release with inspiration (54%), stopping inhalation upon release of the aerosol (24%) (cold Freon effect) and inspiring through the nose whilst actuating the inhaler in the mouth (12%) (Table 1).[25] 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. 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.[27]

Table 1 Frequent errors when using a pressurised metered dose inhaler (pMDI) in patients beginning inhalation therapy for the first time and in patients who already use a pMDI.

pMDI error	Number of patients
No previous pMDI experience ($n = 135$)	
Actuation before inspiration	18
Actuation at end of inspiration	17
Actuation caused stop of inspiration	25
Actuated in mouth but inhaled through nose	14
Others	6
Total	80(59%)
Previous pMDI experience ($n = 1038$)	
Actuation before expiration	1
Actuation before inspiration	35
Actuation at end of inspiration	38
Actuation caused stop of inspiration	27
Actuated in mouth but inhaled through nose	12
Multiple actuations—same inhalation	17
Others	5
Total	135(13%)

Crompton.[25]

Unfortunately, previous ability to correctly use a pMDI is not indicative of correct use during subsequent testing.[25,33] A study from 1976 showed that 14% of patients, who had documented evidence of correct inhaler technique, proved to have totally inefficient coordination of inspiration and dose release when their inhaler use was checked subsequently.[33] Similarly, in a study carried out in 1982,[25] 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 pMDI and were considered to be able to use one of these devices correctly (Table 1). In a large study ($n = 4078$), 71% of patients were found to have difficulty using pMDIs; almost half of the misuers had poor coordination.[5] This inhaler misuse was associated with poor asthma control, with pMDI misusers having less stable asthma control than good users ($p < 0.001$).

Even with the correct inhalation technique, pMDIs are inefficient, often delivering less than 1/3 of the emitted dose to the lungs[34,35] and less than half of the emitted dose to the peripheral airways compared with DPIs,[34,36] with a high proportion of drug being deposited in the mouth and oropharynx[34] which can cause local as well as systemic side effects due to rapid absorption.[37,38] Holding chambers can compensate for many of the problems associated with MDIs such as oropharyngeal drug deposition. Most of these holding chambers are bulky and inconvenient, especially when they need to be carried, which may reduce treatment compliance. Pressurised MDIs also require an optimal inspiratory flow, a full inspiration from functional residual capacity and a breath hold of at least 6 s,[15,16] and so intensive training and regular technique re-testing are necessary.[39] Finally, unlike DPIs, pMDIs have no dose counters or inhalation control mechanisms and, as they use propellant gases and

dispersants, may cause cough, throat irritation and occasionally paradoxical bronchoconstriction.[40]

These observations suggest that the pMDI is a difficult device to use, with many asthmatic patients deriving incomplete benefit from its use. Training apparently results in a more efficient use of pMDIs, but these training sessions must be repeated, and the results checked at regular intervals by a member of medical staff. 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. In order to derive maximum benefit from inhalation therapy, it is necessary to select inhalation devices that are reliable and simple to use by the patients, and provide patient support in order to guarantee high compliance especially with long-term therapy.

Therapeutic improvements due to technical developments

The problem of coordination so regularly seen with pMDIs was addressed in the 1970s and 1980s with the introduction of the spacer device. These devices also reduced the amount of drug deposited in the oropharynx, but they suffered problems with electrostatic charge, needed to be cleaned regularly and were bulky, making them cumbersome to transport.[41] A further advancement in pMDI technology came in the form of a breath-activated pMDI, launched in the UK in 1989, which precluded the need for patients to coordinate device activation with inhalation. These breath-activated inhalers were much easier for patients to use correctly, but the occurrence of the cold freon effect was still possible. By 1995 and the introduction of the Montreal Protocol,[42] use of chlorofluorocarbon (CFC) propellant gases was banned and pharmaceutical companies replaced CFCs with hydrofluorocarbons (hydrofluoroalkanes, HFAs).

The development of the DPI was an important progress in the history of inhalation therapy. In general DPIs are easier to use than most pMDIs. They do not require coordination of inhaler actuation with inhalation. DPIs contain no propellant gases, so they do not produce a cold Freon effect during inhalation and are thus more environmentally friendly. The first DPI appeared on the market in 1969 with the introduction of the Spinhaler® (Fisons, UK), followed by the Rotahaler® (GlaxoSmithKline, UK) in 1977 and the Diskhaler® (GlaxoSmithKline, UK) in 1980. The first multi-dose gravity feed DPI, the Turbuhaler® (AstraZeneca, UK), was introduced in the UK in 1988, followed by the Aerolizer® (Novartis, Switzerland) and the Diskus®/Accuhaler® (GlaxoSmithKline, UK) and in 2001 the Novolizer®(MEDA, Sweden) (Table 2). While the first generation of DPIs had to be cumbersomely re-loaded after each individual dosage, the modern units are easily operated multidose devices.

Limitations of DPIs

DPIs also suffer from some inherent limitations. For example, the Spinhaler®, Rotahaler®, Handihaler® (Boehringer-Ingelheim, Germany) and Aerolizer® require that single doses are individually loaded into the inhaler immediately before use. This is inconvenient for patients and does not allow for direct dose counting. In addition, the inhalation process sometimes has to be repeated until the capsule is empty, which may give rise to underdosing and to high dose variability. These devices contain no inhalation control system and no feedback mechanism which reports effective lung deposition. The Diskhaler® is a multiple unit dose device that has to be repeatedly loaded with a disc of blisters. It needs frequent cleaning. The Diskus® is a 60-dose device that uses a strip of foil drug containing blisters that cannot be reloaded. Common patient errors when using the Diskus® include using a slow inhalation at the start of the inhalation manoeuvre, failure or difficulties to load the device before inhalation and exhaling into the device.[27] The Diskus® has a low intrinsic resistance, but, like the Turbuhaler®, does not have any triggering mechanism which makes optimal drug delivery entirely dependant on an individual patient's uncontrolled inspiratory manoeuvre.

The Turbuhaler® is a multidose or reservoir device. It has several features that can generate uncertainty for both the physician and the patient. There is a relatively high variation in delivered dose,[50,51] and the particle size generated depends on the patients' inspiratory flow rate.[52] It is not easy to use by virtue of its high intrinsic resistance. In addition, patients must inhale sharply through the Turbuhaler® at the beginning of the inhalation manoeuvre to ensure disagglomeration of drug particles and hence effective drug deposition.[52] The device is not refillable, there is no inhalation control mechanism and the dose counter is limited. The amount of drug released from the Turbuhaler® can be reduced in conditions of high humidity.[53] Common patient errors when using the Turbuhaler® include slow inspiration, priming the device at $>45^{\circ}$ from the vertical position, failure to prime or difficulty priming and exhaling into the device.[27]

Factors affecting drug deposition properties of DPIs

Sufficient inspiratory flow

The decisive factor for therapy success with DPIs is the generation of sufficient inspiratory flow to trigger the dosage and disagglomerate the powder to produce drug particles of optimal size to reach the lungs. However, a number of patients are unable to generate sufficient inspiratory airflow to use their DPIs effectively, resulting in poor drug release and low pulmonary deposition. This is particularly the case for older patients (i.e. >60 years), children and those patients with severe airflow limitation. For example, using the 'inhalation manager', which allocates an inhalation manoeuvre to the expected drug delivery values, Kamin et al.[54] showed that as many as 16.7% of patients aged 18–59 years using the Diskus® had an insufficient airflow which almost doubled to 31.5% in older patients (60–99 years). The Turbuhaler® fared less well with 38.9% of 18–59-year olds and 66% of patients aged 60–99 years demonstrating insufficient inspiratory flow.[54] The Novolizer® has a low-to-medium intrinsic airflow resistance, which allows it to be used by most school-aged

Table 2 Summary of Novolizer® clinical trial data.

Patient population	Endpoint	Main findings	Reference
Peak inspiratory flow studies			
Asthmatic children (4–12 years)	PIF	• All children capable of generating sufficient inspiratory flow	Vogelberg et al.[43]
Asthmatic children (6–11 years)	PIF, Novolizer® vs Turbuhaler®	• Generated a higher PIF through the Novolizer® (92.7 vs 68.9 L/min)	Von Berg et al.[44]
Lung deposition			
Healthy adult volunteers	% Lung deposition *in vivo*, Novolizer® vs Turbuhaler®	• At similar inspiratory flows, the Novolizer® and Turbuhaler® achieve similar lung deposition • When used optimally, the Novolizer® deposits more drug in the lung and less in the mouth than the Turbuhaler®	Newman et al.[34]
Efficacy			
COPD patients	Efficacy of salbutamol, Novolizer® vs pMDI	• Novolizer® and pMDI therapeutically equivalent in terms of improvement in lung function (21.3% vs 19.7% max % increase in FEV_1) • 78% patients rated Novolizer® as very good/good compared with 69% in pMDI group • Of previous pMDI users, 78% would rather use a Novolizer®	Kunkel and Chuchalin[45]
Asthmatic patients	Efficacy of budesonide, Novolizer® vs Turbuhaler®	• Equivalent efficacy in terms of FEV_1 improvement	Kunkel and Chuchalin,[45] Chuchalin et al.[46]
Asthmatic patients	Efficacy of budesonide, Novolizer® vs Aerolizer®	• Equivalent efficacy in terms of bronchodilating effect • Duration of action: ⩾12 h for both devices	Richter et al.[47,48]
Asthmatic patients, PMS study	Efficacy, tolerability and acceptance of the Novopulmon® Novolizer®	• Improved lung function • Reduced symptom severity • Majority of patients preferred the Novolizer® of a pMDI or other DPI • Likely to improve compliance	Möller et al.[49]

DPI: dry powder inhaler; FEV_1: forced expiratory volume in 1 s; PIF: peak inspiratory flow; PMS: post-marketing surveillance; pMDI: pressurised metered dose inhaler.

children, elderly patients and those with severe airflow obstruction.[43,47,48]

Dependency of particle size on inspiratory flow

Particle size of drug generated by DPIs is another criterion for success which should be considered as this has implications for drug deposition and clinical efficacy. With DPIs, the respirable particle fraction and consequently drug deposition are dependent on inspiratory flow rate achieved by the patient. This dependency has been clearly shown with the Turbuhaler®.[52] If patients inhale maximally through the Turbuhaler® at the beginning of the inhalation manoeuvre, most of the emitted particles are between 1 and 6 μm in diameter and so would be deposited within the lungs. However, if patients inhale slowly at first and then gradually increased the force of their inhalation as they progress, then the size of emitted particles increases. In this scenario, most of the particles are too large to inspire and so would be deposited in the mouth and oropharynx.[52]

Furthermore, the significance of the inhalation speed seems to vary with the particle size.[55] While small particles (i.e. 1.5 μm particle diameter) have a comparable effect on the forced expiratory volume in 1 s (FEV_1) regardless of the inhalation speed, larger aerosol particles (i.e. 3 and 6 μm

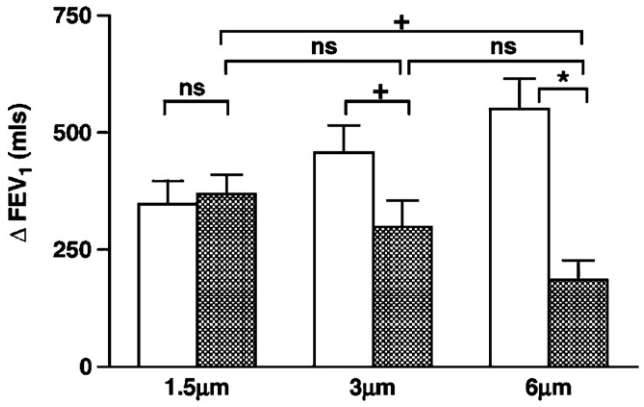

Figure 2 Effect of fast inhalation (shaded bars) compared with slow inhalation (white bars) on forced expiratory volume in 1 s (FEV_1). $^{*}p<0.001$; $^{+}p<0.05$; ns = not significant. Reprinted with permission from Usmani et al.[55]

diameter) exert a greater bronchodilator effect when inhaled at a slower speed (Figure 2).[55] Slow inhalation speed also resulted in a higher drug penetration index regardless of drug particle size.[55] This problem is avoided with the Novolizer® since the flow trigger valve system releases drug powder only after a preset flow rate has been achieved (35 L/min).[56,57]

Ideal particle size?

The situation is further complicated by the discovery that ideal particle size can vary depending on the inhaled active ingredient class. Particle size can be adjusted to improve delivery past the vocal cords. This could lead to a reduction in the oral bioavailability. Theoretically, it could be more important for beclomethasone than for fluticasone to have a smaller MMAD. In addition, although a particle size that increases more peripheral deposition might be desirable to improve efficacy a clear clinical benefit has never been demonstrated for this. Finally, an improved peripheral deposition could raise safety concerns in patients with minimal obstruction.[58]

The complexity of the issue of particle size is further highlighted by the fact that β_2-mimetics should ideally be separated into relatively large aerosol particles (>3–$6\,\mu m$), which are mainly deposited in the large respiratory pathways where this substance class achieves its greatest effect.[55] Simultaneously, this could minimise the risk of systemic side effects, since unlike larger particles, small particles ($<2.5\,\mu m$ diameter) are deposited mainly in the alveoli where they exert no pharmacodynamic effect and are rapidly absorbed, thus increasing the risk of systemic adverse events.[59] By comparison, it would probably be beneficial to generate smaller particles in the case of the ICS in order to reach the peripheral lung regions. Therefore, altering intrapulmonary deposition through aerosol particle size could enhance inhaled drug therapy and might have clinical implications for developing future inhaled treatments. The clinical relevance of this hypothesis is not yet proven and should be further examined in studies.

Requirements for an ideal inhalation system

Fifty years of experience with inhalation systems has enabled the concept of an ideal inhaler device to be formulated.

1. Simple handling is a mandatory requirement—particularly for children.
2. An inhalation unit should possess control mechanisms which ensure:
   (a) optimal respiratory flow at the time at which the dosage is triggered
   (b) a correct inhalation manoeuvre and
   (c) allow the patient to verify successful completion of the inhalation manoeuvre.
3. Both the released active ingredient dosage and the deposition of the active ingredient in the lungs must be sufficiently high and reproducible.
4. There is a need for a dosage counter that counts not only the dosages but also the correctly executed inhalations. This characteristic would allow one to supervise compliance.
5. For reasons of environmental compatibility, modern units should be free of propellant gas and be refillable.
6. According to the GINA guidelines maintenance requirements must be minimal.[1]
7. Patient device preference should also be taken into account.[23]

When selecting an inhalation device for a patient it is useful to ask oneself the following questions[60]:

1. In what device is the desired drug available and affordable for the patient?
2. Who will teach the patient the correct inhalation technique?
3. Does the patient have a preference for one type of device, assuming that the device/drug combination is available, affordable and can be handled correctly by the patient after education?

When selecting an inhalation unit for an individual patient, it is necessary to consider whether sufficient inspiratory flow or an effective vital capacity manoeuvre is possible for this patient (Figure 3). If the answer to this question is 'yes' then an inhalation from a DPI would be the device of choice or, alternatively, a breath-actuated HFA-pMDI, possibly in combination with a spacer. If the patients do not have a sufficient inspiratory capacity a nebuliser or an HFA-pMDI and spacer with a valve are the more suitable choice (Figure 3).[61] Additionally, if possible, different medications should be delivered from identical devices. If individual combination therapy is unavoidable, combinations of DPIs are preferable to an MDI and a DPI.[62] Ideally, the prescribed inhaler should have a low-to-medium airflow resistance and require minimal patient coordination. Patient preference should also be taken into account where there is a choice among several different inhalation systems. Patients who have actively participated in and have confidence in their inhaler choice are more likely to use it regularly and correctly.

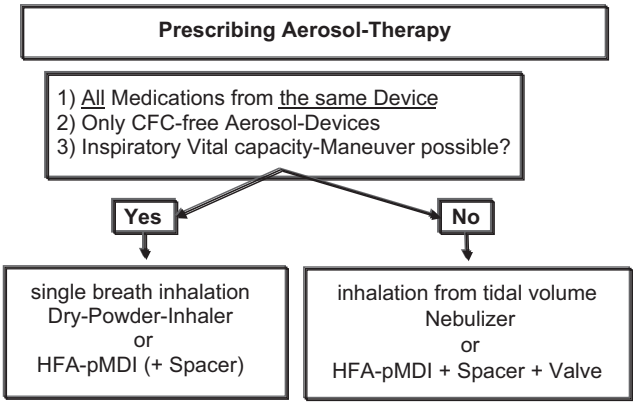

Figure 3 Prerequisites for the selection of an inhalation system in an individual patient.

Mechanisms that can improve correct inhalation

The requirements that, according to the authors' opinion, are helpful to support optimal drug delivery from a metered dose inhaler include that the device be breath-activated, multidose and refillable with an inhalation control system which indicates indirectly that deposition of the therapeutic agent in the lungs has occurred. This can be achieved with a flow trigger valve, which allows activation of the device and releases the drug only when the required inspiratory flow necessary for drug deposition in the lower airways is reached.[57] In addition, a dose meter that counts only correctly performed inhalations might offer an advantage to monitor patient compliance than one that records each actuation of the device irrespective of whether the durg has been properly inhaled or not. These features can overcome some of the pitfalls of a poor patient inhalation technique and poor patient compliance.

Conclusions

Improvements in the effectiveness, selectivity and safety of inhaled pharmacological therapies have not yet produced a concomitant improvement in asthma and COPD control. In the near future, it seems unlikely that improvements in disease control will be due to the introduction of new and novel therapies, but rather from improvements in how these pharmacological agents are delivered to the lung (i.e. improvements in inhaler technology and design). The problems associated with pMDI use have been well-documented. DPIs overcome many of the problems inherent in pMDI design, but suffer from limitations of their own, most notably a dependency on patients' inspiratory flow to generate an fine particle fraction suitable for deposition in the lungs. When choosing an inhaler device for an individual patient, it is important to check if patients are capable of generating sufficient inspiratory flow, and where possible to prescribe the same device to deliver all a patient's medication. Features of devices that help the patient to perform correct inhalation assure drug delivery to the lungs. Advanced devices may help to improve patients' compliance and thus improve asthma control.[49]

Conflict of interest statements

J.C.V. has lectured for and/or sits on Advisory Boards for Altana/Nycomed, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, MEDA, Merck/MSD, Mundipharma, Novartis, Pfizer, Sandoz/Hexal and SchwarzPharma, all of which have an interest in inhaled drug delivery.

G.K.C. has lectured for and/or sits on an advisory board for MEDA, which has an interest in inhaled drug delivery.

R.D.N. has no conflict of interest to declare.

S.P. has consultant arrangements with GlaxoSmithKline, Nycomed and Merck and has received grants/research support from GlaxoSmithKline, Nycomed and AstraZeneca, all of which have an interest in inhaled drug delivery.

A.M. has given lectures for MSD, AstraZeneca, Stallergenes, Novartis and Boehringer, and sits on Advisory Boards for Novartis and Meda-Pharma, all of which have an interest in inhaled drug delivery.

J.S. has lectured for Novartis, MEDA, GlaxoSmithKline and AstraZeneca, all of which have an interest in inhaled drug delivery.

P.B. receives research funding and sits on Advisory Boards for Altana/Nycomed, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis and Pfizer, all of which have an interest in inhaled drug delivery.

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