Inhaled corticosteroid delivery systems: clinical role of a breath-actuated device

D. DONNELL

Abstract. – Several devices have been developed to overcome the need to coordinate actuation with inhalation required during use of a pressurised metered dose inhaler (MDI) and to improve drug delivery to the lung. These include spacer attachments for MDIs, dry powder inhalers and breath-actuated MDIs.

The breath-actuated Autohaler™ (3M Pharmaceuticals) is a compact, multidose inhaler device that, unlike dry powder inhalers, does not rely on the patient’s inspiratory effort to aerosolise the dose of medication. Due to its simple operation, the Autohaler is suitable for patients unable to operate a conventional MDI efficiently, including the elderly, children, patients with arthritis and patients with low inspiratory flow rates.

The mandatory replacement of chlorofluorocarbon propellants with non-ozone-depleting propellants has given the opportunity to improve drug delivery characteristics of MDIs. Recently, a formulation of beclomethasone dipropionate in hydrofluoroalkane-134a (HFA-BDP), has been developed in a conventional MDI that delivers most of the emitted dose to the lung. Drug deposition studies show that the HFA-BDP formulation in the Autohaler device has a similar lung deposition pattern to drug delivered from the MDI, when used correctly, and dose delivery is consistent across a wide range of inspiratory flow rates. Furthermore, HFA-BDP Autohaler has similar clinical benefits to CFC-BDP Autohaler but at less than half the dose. HFA-BDP Autohaler offers a useful CFC-free delivery option for patients challenged by the conventional MDI device.

Key Words: Corticosteroids, Inhaler devices, Autohaler.

Introduction

Recognition that asthma is a chronic inflammatory disorder of the lungs has led management guidelines to recommend the first-line use of inhaled corticosteroids. By reducing airway inflammation and airway hyper-reactivity, inhaled corticosteroids effectively control asthma symptoms and improve lung function. Inhaled therapy offers a major advantage over oral corticosteroid administration in that medication can be delivered via an inhaler device directly to the site of action with less risk of unwanted systemic effects. However, successful asthma management relies on patients to administer their treatment correctly on a regular basis. Lack of patient compliance or faulty inhaler technique can ultimately lead to poor control of asthma symptoms and potentially fatal acute exacerbations.

This article reviews the issues encountered during the clinical use of each type of inhaler device, with particular regard to drug delivery and ease of use, and considers the role of a breath-actuated inhaler containing beclomethasone dipropionate (QVAR™ Autohaler™ aerosol, 3M Pharmaceuticals).

Metered Dose Inhalers

Since their introduction in the late 1950s, press and breathe metered dose inhalers (MDIs) have revolutionised the treatment of asthma and are the most commonly prescribed method of delivering inhaled corticosteroids. MDIs are compact, portable, pressurised systems that deliver multiple doses of drug formulated in liquid propellant. Upon actuation, a regulated measure of medication is released and the propellant aerosolises the drug component into particles suitable for inhalation, through the mouth.

Drug delivery into the lung is influenced by the complex interaction between the physical characteristics of the aerosol spray, airflow,
airway morphology and pathology, as well as inhalation technique. Correct MDI use requires several co-ordinated manoeuvres, but with estimates of misuse ranging from 12% to 89%, it is evident that many patients find this difficult to achieve. The most common problem is synchronising the actuation of the inhaler device with slow inspiration. Poor co-ordination can result in medication being released either too early or too late in the inspiration cycle, or in the extreme, one action being performed without the other. Other types of problems encountered with MDIs include inhaling too rapidly, inadequate duration of breath holding, and the cold-freon effect, where the patient stops inhaling as soon as the cold propellant spray hits the back of the throat. Physical incompetence with an MDI is a particular concern for the elderly and arthritic, who often lack the hand strength and finger dexterity necessary to actuate an MDI device.

The most obvious consequence of variability of drug delivery resulting from a faulty inhaler technique is sub-optimal corticosteroid therapy and an increased risk of losing control of asthma symptoms or experiencing asthma exacerbations. To improve drug deposition in the lung and overcome the difficulties with co-ordination, several devices have been developed, including spacer attachments for MDIs and a range of dry powder inhalers. A further solution has been the introduction of a breath-actuated MDI, and more recently, with the mandatory replacement of chlorofluorocarbon (CFCs) propellants, the development of a non-CFC breath-actuated MDI containing beclomethasone dipropionate (QVAR™ Autohaler™ aerosol).

Metered Dose Inhalers Plus Spacer

Immediately following actuation of the conventional MDI in the mouth, the combination of high propellant velocity (> 30 m/sec) and initially large-sized aerosol particles (mass median aerodynamic diameter > 10 µm) increase the likelihood of drug deposition in the oropharynx, rather than drug reaching the site of action within the lungs. The attachment of a spacer device or holding chamber to the MDI compels patients to inhale at some distance from the actuator, thereby allowing time for the spray front to slow down and larger particles to deposit on the chamber walls. By this function, oropharyngeal deposition of corticosteroids is reduced, limiting local side effects such as oral candidiasis and dysphonia, but it is debatable as to whether or not spacers improve drug delivery to the airways. Inconsistency between studies is confounded by the observation that spacers offer no additional benefit to patients demonstrating a good inhaler technique. Furthermore, electrostatic charge in plastic spacers tends to retain drug particles on the inner walls of the device thereby reducing drug availability.

Dry Powder Inhalers

Designed as breath-actuated devices to overcome the need to include chlorofluorocarbon (CFC) propellants in the formulation, dry powder inhalers (DPIs) have some inherent problems of their own. In DPIs, the corticosteroid drug is in the form of microfine particles loosely held in aggregates. The airstream created during inspiration is not only required to release the dose from the device but is essential in aerosolising the particles into a respirable size range. Consequently, both the emitted dose and the particle size distribution are subject to individual variation dependent upon the patient’s inspiratory effort. In clinical practice, this can translate into less lung deposition in a patient with severe airflow obstruction and limited ability to inspire than in a patient able to generate greater inspiratory flow rates.
Considering DPIs require the patient to produce sufficient inspiratory flow to ensure drug delivery into the bronchopulmonary tree, they may be regarded as having “breath-dependent” delivery.

Another potential concern inherent in DPIs, is the susceptibility of powders to become more cohesive at high humidity, thereby reducing drug output. However, the problem of inconveniently having to load each dose in earlier single-dose DPI devices has been overcome by the introduction of several multidose devices.

The Breath-Actuated Autohaler™ Device

Design of the Autohaler device

A further innovation to eliminate the need to co-ordinate manual actuation and inhalation has been the development of a breath-actuated MDI, the A utohaler. To prime the A utohaler, the patient simply lifts a lever on the top of the actuator body, which applies pressure on the canister via a spring mechanism (Figure 1). The canister is blocked from moving under this pressure by the triggering mechanism resting on a vane located behind the mouthpiece. When the patient inhales through the mouthpiece, the vane rotates, activating the triggering mechanism and releasing the drug. Importantly, however, because the A utohaler device uses a pressurised propellant system, dose delivery is actuated with an inspiratory flow of 30 L/min or more. Dose delivery does not alter with increasing inspiratory effort. A further design feature of the A utohaler is the audible “click” on actuation that serves to reassure the patient that the medication has been dispensed.

More recently, the mandatory replacement of chlorofluorocarbon propellants has initiated reformulation of conventional and breath-actuated MDIs and presented an opportunity to improve their performance, by delivering more corticosteroid drug in the lungs and less in the oropharynx. With these concepts in mind, new formulations of beclomethasone dipropionate in hydrofluoroalkane-134a, a non-ozone depleting propellant, have been developed both in conventional (HFA-BDP; QVAR™, 3M Pharmaceuticals) and breath-actuated A utohaler devices (HFA-BDP A utohaler; QVAR™ A utohaler™, 3M Pharmaceuticals).

Inhalation technique

Not having to synchronise actuation and inhalation, administration from the A utohaler is simplified and allows patients to focus on inhalation manoeuvres necessary to optimise drug delivery, such as slow and deep inhalation and breath holding. The breath-actuated mechanism of the A utohaler is triggered early in the inspiratory cycle at low inhalation flow rates of approximately 30 L/min. Since drug deposition of a pressurised aerosol appears to be greatest when actuation occurs in the early phase of inspiration, the A utohaler should enhance pulmonary delivery in patients who have difficulty synchronising actuation with inhalation. Indeed, drug deposition in the lungs from the A utohaler is equivalent to that obtained with a correctly used conventional press and breathe MDI.
Recently a formulation of HFA-BDP (QVAR™; 3M Pharmaceuticals) has been introduced that, compared with CFC-BDP, has a smaller particle size and a softer, warmer, slower spray, resulting in improved lung deposition (50-60% vs. < 10%) and reduced oropharyngeal deposition (30% vs. > 90%)33. HFA-BDP has also been developed in the A utohaler device (HFA-BDP A utohaler; QVAR™ A utohaler™; 3M Pharmaceuticals). Lung deposition from the HFA-BDP A utohaler provides similar lung deposition as an optimally used conventional HFA-BDP press and breathe inhaler (56% vs. 58%; Table I) and dose delivery is consistent across a wide range of inspiratory flows (26-137 L/min)33. A pharmacokinetic study in children with asthma, using activated oral charcoal to block gut absorption, has shown the early systemic bioavailability (as C_{max}) of HFA-BDP A utohaler 200 µg was 1.5-fold greater than CFC-BDP 400 µg plus a large volume spacer34. This suggests that the relative lung dose in children is 3-fold higher with the HFA-BDP A utohaler 200 µg than the CFC-BDP 400 µg via a spacer.

Ease of use

Due to its simple operation, the A utohaler offers a useful alternative to conventional M DIs with add-on spacer devices or dry powder inhalers for patients with inadequate inhaler technique. The use of the A utohaler has been tested in a number of patient populations, including first-time and previous users of inhalers, the elderly, children, patients with arthritis and patients with low inspiratory flow rates35-45.

Operating the A utohaler device

In a study involving subjects who had never previously used any type of inhaler, after following the written instructions provided with the A utohaler, 63% of individuals were able to operate the inhaler efficiently35. When additional verbal instruction was provided, 91% of the group could use the device correctly. This was in contrast to the situation with a conventional press and breathe M DI, where only 39% of subjects could operate the inhaler competently after reading written instructions, and only 50% of subjects were proficient after receiving additional verbal instruction. Among asthma patients with a poor conventional inhaler technique, a correct A utohaler technique was demonstrated in 43% of users after reading written instruction alone and in 82% of users after receiving verbal explanation36. In another study, patients were asked about the ease of use of the A utohaler, and 74% found the device easy to use and 76% expressed it was easier to use than other inhaler types37.

Elderly and subjects with limited manual dexterity

A adequacy of A utohaler inhalation technique compared with a conventional M DI and a dry powder inhaler in elderly and/or arthritic subjects has been investigated in several studies38-40. Two studies involving elderly populations found more patients successfully demonstrated a correct inhaler technique for the breath-actuated inhaler than for either the conventional M DI or Rotahaler®, a dry powder inhaler38,39. Similarly, a study comprising patients with limited manual dexterity found 70% of the group could use the A utohaler easily, in comparison with 54% for the Rotahaler and 46% for the Diskhaler® (both dry powder inhalers), and 40% for the conventional M DI40.

Children

Following instruction, children aged 3 to 13 years have been able to demonstrate an effective A utohaler technique41-43. A fter demon-

<table>
<thead>
<tr>
<th>Time to actuate (sec)</th>
<th>Lung (%)</th>
<th>Mouth (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A utohaler</td>
<td>0.2</td>
<td>56</td>
</tr>
<tr>
<td>M DI co-ordinated</td>
<td>0.4</td>
<td>58</td>
</tr>
<tr>
<td>M DI early</td>
<td>- 0.5</td>
<td>34</td>
</tr>
<tr>
<td>M DI late</td>
<td>2.5</td>
<td>32</td>
</tr>
</tbody>
</table>

*A s a percentage of the ex-actuator dose.

Data derived from reference 33.
istration with a placebo inhaler device, 20% of a group of 3 to 6 year olds had a satisfactory Autohaler technique and after further instruction, this increased to 75%, emphasising the importance of adequate training. Among a group of children with asthma aged between 4 and 13 years hospitalised with acute exacerbations, 99% of Autohaler actuations were successful compared with 74% of actuations from a dry-powder device.

**Patients with low inspiratory airflow**

Because the Autohaler is activated at low inspiratory flow rates it can be used in patients with relatively severe airflow obstruction. Two clinical studies have shown patients with severe airflow limitation (defined as forced expiratory volume at 1 second \( \text{FEV}_1 \) of \( \leq 1 \) L and a peak expiratory flow \( \text{PEF} \) of \( \leq 200 \) L/min) were able to activate the Autohaler device. In one study 29 of 30 patients (97%) were able to activate the Autohaler, while in the other study 151 of 156 patients (96.8%) actuated the device on the first or second attempt.

**Patient preference**

Many patients who had previously experienced co-ordination difficulties or had functional limitations with conventional MDIs expressed a preference for the Autohaler device. The results of a comparison of a conventional MDI with and without a spacer and the Turbuhaler, a dry powder inhaler, were that most patients found the Autohaler easier to use on a regular basis.

**Clinical efficacy: the Autohaler device versus conventional MDIs**

The therapeutic equivalence of the bronchodilatory action of beta-agonists such as salbutamol and pirbuterol when delivered from the Autohaler or a conventional MDI has been demonstrated in two clinical studies, involving adults or children. Similar improvements in lung function (\( \text{FEV}_1 \), forced expiratory flow rate between 25% and 75% of vital capacity [\( \text{FEF}_{25-75} \)], and forced vital capacity [\( \text{FVC} \)]) of adult asthmatics after treatment with pirbuterol were observed when medication was inhaled from the A Autohaler or an optimally operated conventional MDI. A I, in children aged between 6 and 14 years correctly using either device, the bronchodilatory effect of salbutamol given via the A Autohaler was similar if not greater than the effect following administration from the MDI.

The clinical response to inhaled corticosteroids from different delivery devices is confounded by many factors. To allow correct interpretation and comparison of the therapeutic effect of beclomethasone dipropionate delivered from the Autohaler device or a conventional MDI, a randomised, double-blind, double-dummy, crossover design was used. A also, patients included in the study were stable on inhaled corticosteroid therapy and demonstrated a proficient MDI inhalation technique. Each inhaler device was used for two weeks and patients maintained the same dose of medication throughout the study. Data revealed that treatment with beclomethasone dipropionate was clinically equivalent when delivered by the A Autohaler or a conventional MDI used efficiently, as measured by lung function (\( \text{FEV}_1 \) and \( \text{PEF} \)), subjective symptom score and bronchodilator requirement.

An HFA-BDP formulation in a conventional MDI (QVAR™, 3M Pharmaceuticals) that significantly reduces oropharyngeal deposition and improves drug delivery to all inflammatory sites throughout the bronchopulmonary tree, has shown therapeutic equivalence to CFC-BDP but at half the nominal dose. The HFA-BDP formulation in the Autohaler has a similar lung deposition pattern to the HFA-BDP MDI, and has demonstrated similar clinical benefits to CFC-BDP Autohaler but at less than half the dose.

In a double-blind, double dummy, randomised, parallel group study, HFA-BDP A Autohaler 400 µg daily was shown to be as equally effective as CFC-BDP A Autohaler 1000 µg daily in controlling asthma symptoms and lung function in patients with moderate persistent asthma. Furthermore, there was no difference between treatment groups in airway hyperresponsiveness and serum markers of inflammation.

**Clinical efficacy: the Autohaler device versus DPIs**

Therapeutic response to drug delivery from the A Autohaler has also been compared
with that from dry powder inhalers. A randomised, double-blind crossover study in children with asthma demonstrated similar improvements in lung function (PEF) after salbutamol was delivered from either inhaler device, but more children were able to activate the Autohaler more consistently than the Rotahaler.

Clinical response to inhaled corticosteroid delivered from either the Autohaler or Turbuhaler devices was studied in a randomised, open-label crossover study in adult patients with stable asthma symptoms. Overall therapeutic equivalence of asthma control (FEV₁, morning and evening PEF, and night-time symptoms) was demonstrated using an equivalent dose of inhaled corticosteroid from each device. However, a greater proportion of patients was confident in dose delivery from the Autohaler device as perceived by feeling and hearing dose release. Unlike the immediate symptomatic relief from inhaled bronchodilators providing reassurance of dose delivery, no such perception is apparent for inhaled corticosteroids where compliance to regular prophylactic therapy is essential for maintaining asthma control. These findings have implications for patient compliance, as confidence in inhaler use and dose delivery may affect long-term compliance to inhaled corticosteroid therapy.

Interestingly, a retrospective analysis of asthma-related prescribing patterns showed the mean daily inhaled corticosteroid dose prescribed from the Autohaler was lower at 569 µg/day compared with the Diskhaler (638 µg/day), conventional MDI (665 µg/day) and Turbuhaler (990 µg/day) devices. This may reflect the consistency of dose delivery to the target organ for patients using the Autohaler. The
introduction of the HFA-BDP A utohaler has offered a further opportunity to lower daily inhaled corticosteroid doses without compromising asthma control in comparison with the dose of budesonide delivered by the Turbuhaler device (BUD-TH). Asthma patients symptomatic on their current inhaled steroid dose were randomised to receive daily doses of HFA-BDH A utohaler 400 µg or BUD-TH 800 µg (mild-to-moderate asthma), or HFA-BDH A utohaler 800 µg or BUD-TH 1,600 µg (moderate-to-severe asthma) in line with Global Initiative Guidelines for Asthma (GINA)53. In both treatment groups, HFA-BDP A utohaler at half the daily dose of BUD-TH produced equivalent improvement in control of asthma (Figure 3), but gave significantly greater improvement in patients with severe symptoms (Figure 4). While the pharmacokinetic and biochemical parameters of BUD and BDP are diverse, the efficacy results may partly be attributed to the lung deposition pattern of HFA-BDP A utohaler producing greater drug penetration into the lung periphery33.

Cost-effectiveness

Ever growing pressure for cost containment in healthcare expenditure has focussed attention on the economic burden of managing chronic diseases such as asthma. Although suboptimal therapy with conventional MDIs has well-documented clinical consequences, such patients may also incur higher medical costs through more frequent physician-visits or hospitalisations, or increased use of medication for symptomatic relief54. A recent retrospective cost analysis using data from a pharmacy and medical claims database indicated that the total cost savings associated with the use of the A utohaler device as opposed to a conventional MDI ranged from 8.7% to 11.7%55. Cost effectiveness can also be considered in respect to drug utilisation, where compared to a conventional MDI, the A utohaler has been shown to reduce drug usage by 23%54.

Conclusion

Selection of the most appropriate inhaler device for an individual patient must necessarily be based on clinical indications, patient preference and ability to use the inhaler, therapeutic response and cost. Although, the con-

Figure 3. Mean change from baseline in morning PEF after 3 and 8 weeks of treatment with HFA-BDP A utohaler 800 µg/day or budesonide Turbuhaler 1600 µg/day53.
conventional MDI is the most frequently prescribed inhaler for delivering inhaled corticosteroids, some patients have difficulty in synchronising the actuation of the device with inspiration, and require an alternative delivery method.

The breath-actuated Autohaler is a compact, multidose inhaler device that, unlike dry powder inhalers, does not rely on the patient’s inspiratory effort to aerosolise the dose of medication. Due to its simple operation, the Autohaler is suitable for patients unable to operate a conventional MDI efficiently, including the elderly, children, patients with arthritis and patients with low inspiratory flow rates.

The mandatory replacement of chlorofluorocarbon propellants with non-ozone-depleting propellants has given the opportunity to improve drug delivery characteristics of MDIs. Recently, a formulation of beclomethasone dipropionate in hydrofluoroalkane-134a (HFA-BDP) has been developed in a conventional MDI that delivers most of the emitted dose to the lungs. Drug deposition studies show that the HFA-BDP formulation in the Autohaler device has a similar lung deposition pattern to drug delivered from the MDI, when used correctly. However the advantage is that dose delivery is consistent across a wide range of inspiratory flows rates. HFA-BDP A Autohaler offers the patient all the therapeutic benefits associated with using an extra-fine aerosol but in addition its design provides a useful delivery option for patients challenged by other inhaler systems.

References

Inhaled corticosteroid delivery systems: clinical role of a breath-actuated device


37) Bronsky EA, Malden D, Pijet JC et al. Ease-of-use study of pirbuterol acetate in the Autohaler™ actu-


44) WALLACE WAH, LENNY J, COOKSEY E et al. Ability of patients with severe airflow limitation to trigger a new breath actuated inhaler. Thorax 1989; 44: 341P.


