Factors guiding the choice of delivery device for inhaled corticosteroids in the long-term management of stable asthma and COPD: Focus on budesonide

Lars Thorsson\textsuperscript{a,}* , David Geller\textsuperscript{b}

\textsuperscript{a}AstraZeneca R&D, Experimental Medicine, 221 87 Lund, Sweden
\textsuperscript{b}The Nemours Children’s Clinic, Orlando, FL, USA

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\textbf{Summary} Inhaled corticosteroids (ICSs) have become the mainstay of chronic controller therapy to treat airways inflammation in asthma and to reduce exacerbations in chronic obstructive pulmonary disease. An array of ICSs are now available that are aerosolized by a range of delivery systems. Such devices include pressurized (or propellant) metered-dose inhalers (pMDIs), pMDIs plus valved holding chambers or spacers, breath-actuated inhalers, and nebulizers. More recently, dry-powder inhalers (DPIs) were developed to help overcome problems of hand–breath coordination associated with pMDIs.

The clinical benefit of ICSs therapy is determined by a complex interplay between the nature and severity of the disease, the type of drug and its formulation, and characteristics of the delivery device together with the patient's ability to use the device correctly.

The ICSs budesonide is available by pMDI, DPI, and nebulizer—allowing the physician to select the best device for each individual patient. Indeed, the availability of budesonide in three different delivery systems allows versatility for the prescribing physician and provides continuity of drug therapy for younger patients who may remain on the same ICSs as they mature.

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\textbf{Introduction} Asthma and chronic obstructive pulmonary disease (COPD) are common respiratory conditions that have a major impact on society in terms of morbidity, mortality, and costs. They are characterized by
chronic inflammation of the airways associated with variable airflow limitation. The worldwide prevalence of both diseases is increasing, together with the concomitant implications for the health of the population and the cost to society.1,2

Anti-inflammatory and bronchodilator medications for asthma and COPD are delivered by inhalation to the affected sites—the airways and lungs. Topical application of these drugs to the lung maximizes efficacy and minimizes potential side effects. Inhaled corticosteroids (ICSs) are more effective than cromones or leukotriene modifiers in the control of asthma and are now regarded as the preferred therapy for patients with mild, moderate, or severe persistent asthma.3,4 In addition, a variety of delivery systems are used to target ICSs to the airways, including pressurized (or propellant) metered-dose inhalers (pMDIs), pMDIs plus valved holding chambers or spacers, breath-actuated MDIs, dry-powder inhalers (DPIs), and nebulizers.

The primary objective of ICSs therapy in patients with asthma or COPD is to deliver sufficiently high concentrations of the drug to the bronchial mucosa, while minimizing the amount of drug reaching the systemic circulation and thus reducing the potential for adverse systemic and local side effects. Many factors influence the distribution of an aerosolized drug throughout the tracheobronchial tract and its subsequent metabolic fate and therapeutic effects. These factors can be divided into three major categories (Table 1):

- drug- and formulation-related factors;
- device-related variables;
- patient- and disease-related factors.

A range of delivery devices have been developed to address the different clinical circumstances and patient types receiving ICSs treatment. The clinical benefit of therapy is affected by the nature and extent of the patient’s disease, the drug and formulation, the characteristics of the device, and the patient’s ability to use the device correctly. An understanding of these factors is necessary when considering the most appropriate treatment option. The aim of this review is to examine the key factors influencing the relative clinical efficacy and safety of the different inhalation systems for the delivery of corticosteroids to patients with asthma and COPD, and thus help guide selection of the most appropriate delivery device for the individual patient.

Throughout this review, the corticosteroid, budesonide, has been used as an example to explain the impact of these factors using various delivery devices. Budesonide has been selected for this role in view of the extensive evidence demonstrating its efficacy in the treatment of persistent asthma across all age groups.5

### Delivery options for inhaled corticosteroids

pMDIs consist of a pressurized aerosol canister that contains the medication either dissolved or suspended in liquefied gas propellant(s), together with surfactants and other excipients, such as preservatives and flavourings. A metering system controls the volume of drug mixture that is released when

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Abbreviation: pMDIs, pressurized metered-dose inhalers.
the actuator is pressed. The propellant that forms the aerosol has historically been a chlorofluorocarbon (CFC), but due to environmental concerns, they are gradually being replaced with hydrofluorocarbons (HFCs). Most HFA formulations have a gentler plume (slower particle velocity) and the solution HFA formulations have reduced particle size that can dramatically influence lung deposition vs. a CFC suspension. About 80–90% of the ICSs dose from a CFC-pMDI is deposited in the oropharynx where it can cause local side effects. Furthermore, a major limitation of pMDIs is that they require coordination of actuation and inhalation. Effective patient instruction, including practice with a placebo device, is therefore essential. Patients may also have difficulty using the mouthpiece of the actuator, and the cold temperature of the aerosol when it hits the back of the throat may cause the user to interrupt inhalation (known as the “cold Freon® effect”).

A host of add-on devices for pMDIs have been designed to overcome these limitations. Spacers and valved holding chambers are designed to reduce high oropharyngeal drug deposition and eliminate the cold Freon® effect. Valved holding chambers can also reduce drug loss caused by poor hand-breath coordination. Breath-actuated or flow-triggered pMDIs were developed to overcome the need for hand-breath coordination. However, these devices still require a proper technique when used with a slow inhalation and a breath-hold, which may be difficult for some patients, particularly young children. Therefore, valved holding chambers with face masks are available for infants and young children and are used with tidal breathing.

DPIs offer an alternative response to the difficulties associated with pMDIs, and are actuated and driven by inspiratory flow. These devices create the aerosol by passing air from the inspiratory effort through medication formulated as a dry powder. The active ingredient is in the form of micronized drug particles that can be mixed with larger glucose or lactose particles, or bound into loose aggregates. Micronized particles tend to adhere strongly to each other and to most surfaces, and disaggregation must occur for the drug to be delivered effectively. Disaggregation occurs during inhalation when the powder is broken up into its constituent particles by turbulent airflow and/or mechanical devices, such as screens or spinning surfaces. One type of DPI is Turbuhaler™, which is routinely used for the delivery of asthma medication. Turbuhaler™ has a built-in resistance in the form of a spiral-shaped air passage that promotes the separation of the dry-powder microaggregates of drug into particles of respirable size before they leave the inhaler. However, with this formulation it is important to educate the patient that the aerosol has no flavour, otherwise the patient may be unsure whether a dose was delivered by the device.

Nebulizers have been available in one form or another for over a century. They produce a fine mist of droplets that contains the active drug. Nebulizers are a practical means of administering inhaled medications to very young children and patients who are unable to use other inhaler devices. They are also used in preventive and emergency contexts. There are two classic types of nebulizers, which are classified according to how they produce the droplets. Jet nebulizers use a source of compressed air forced through a small orifice, forming an air jet that transforms a liquid into primary aerosol droplets. The larger particles impact on internal baffles and are recirculated, while the smaller particles exit the nebulizer and are available for inhalation. Ultrasonic nebulizers produce the droplets by mechanical vibration of a piezoelectric plate, creating a geyser or fountain effect from which particles of the liquid are created. The former type is less complex, cheaper and therefore more commonly used. The drug is contained in an aqueous solution or as a suspension (Pulmicort Respules® [budesonide]) in which small particles are suspended in the fluid. The mist is then inhaled via a mouthpiece or a face mask. New types of nebulizers, such as those that use vibrating porous membrane technology, are under development and may be useful for both solutions and certain suspensions.

Preclinical and clinical pharmacologic comparison of the delivery options for inhaled budesonide

In vitro characteristics of the device

Aerosol particle/droplet size is one of the most important factors determining the deposition of ICSs in the airways. The portion of an aerosol that has the highest probability of bypassing the upper airway and depositing in the lung measure between 1 and 5 μm. Particles larger than this are generally deposited in the oropharyngeal region and are swallowed, while submicronic particles do not carry much drug and may be exhaled before deposition takes place. Smaller particles tend to deposit more peripherally in the lung than coarser particles, which may lead to a different clinical response. Consequently, differences in particle size of the aerosol emitted from inhalation devices

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may account for some of the variability in therapeutic efficacy and safety of the various ICSs. Measurement of particle size, therefore, has an important role in guiding product development and in quality control of the marketed product.

The distribution of aerosol particle/droplet size can be expressed in terms of either:

- the mass median aerodynamic diameter (MMAD)—the droplet size at which half of the mass of the aerosol is contained in smaller droplets and half in larger droplets;
- the fine particle fraction—the percentage of particles that are \( <5 \mu m \) in diameter.

These measures have been used for comparisons of the in vitro performance of different inhaler device and drug combinations. In general, the higher the fine particle fraction, the higher the proportion of the emitted dose that is likely to reach the lung. Fine particle fraction (and consequently fine particle dose) can be assessed by drawing aerosols through an Andersen multi-stage sampler (an impactor device fitted with a series of filters that collect progressively smaller particles). The inhaler and impactor are connected via an inlet throat. These laboratory assessments of fine particle dose have been shown to correlate well with lung deposition in humans if the traditional inlet throat is replaced with an anatomically accurate replica or cast of the human throat.\(^7\) Interestingly, the choice of inlet throat has a significant effect on the fine particle dose recovered from a pMDI (50% difference in fine particle fraction between throats) but considerably less influence on that recovered from a DPI (15% difference).\(^1^1\) This suggests that in humans, the interaction between the throat and the aerosol cloud is greater for an aerosol generated by a pMDI than for one generated via a DPI.\(^7\)

Using the anatomically correct throat method described above, Olsson\(^1^1\) has shown that the in vitro fine particle dose of budesonide (expressed as a per cent of the nominal dose) via Turbuhaler\(^\text{TM}\) DPI is approximately twice that achieved via a pMDI. Conversely, for fluticasone propionate (hereafter referred to as fluticasone) the opposite appears to be true—i.e. the fine particle dose delivered via pMDI is about twice that via the Diskhaler\(^\text{®}\) DPI.\(^1^1\) This illustrates the point that all inhaled formulations have unique properties; hence, no general conclusions should be made for DPIs, pMDIs, or nebulizers. Figure 1 shows an in vitro comparison (using similar methodology to that described above) of the proportion of the nominal dose of budesonide, beclomethasone dipropionate, or fluticasone delivered as fine drug particles (<\(5 \mu m\)) from four different DPIs at flow rates corresponding to weak, moderate, and strong inspiratory forces.\(^1^1\) Comparable degrees of inspiratory force, rather than identical flow rates, were used since different DPIs offer different resistance to inspiratory flow. These data show that the budesonide Turbuhaler\(^\text{TM}\) device consistently produced a higher proportion of respirable particles than the other devices (even when the inspiratory force was relatively weak), indicating that this device could be considered for patients with relatively low inspiratory abilities.

**Pulmonary/extrapulmonary deposition and inhalation characteristics**

The clinical efficacy and safety of ICSs in asthma and COPD is dependent upon maximizing the proportion of the dose that is delivered to the lungs and airways, while minimizing systemic exposure to the drug. While in vitro assessments of fine particle mass do provide some predictive
information on the behaviour of an aerosolized drug within the tracheobronchial tree, a number of other factors (plume geometry [pMDIs], particle inertia, breathing pattern, inhalation flow, and disease-related changes in airway geometry and flow) also influence pulmonary disposition. Therefore, in vivo deposition studies are also needed to support the in vitro findings.

There are two main methods used to measure aerosol deposition in the lungs. First, γ-scintigraphy is performed by radiolabelling the drug with a substance like 99m-technetium, and scanning the subject after inhalation of the drug. This technique has the advantage of being able to quantify the proportion of aerosol inhaled by the patient, as well as regional distribution in the upper airway and lungs. Second, since most of the ICSs deposited in the lower airways will be absorbed into the bloodstream, pharmacokinetic techniques are used to measure lung deposition. This technique can assess the total amount of ICSs that interacts with the airway epithelium and is absorbed systemically, but will miss the small portion that may be expectorated or swallowed after mucociliary clearance, and cannot tell us about regional distribution. Therefore, γ-scintigraphy and pharmacokinetic studies are complementary, and have both been used for budesonide and other ICSs delivered by nebulizers, MDIs and DPIs.

Deposition studies have shown significant differences between devices with respect to pulmonary deposition of corticosteroids, with values ranging from approximately 5% to over 50% (ex-actuator or delivered dose, respectively) for currently available corticosteroid pMDIs and DPI systems (Table 2). For example, Thorsson et al. reported that lung deposition of budesonide in healthy volunteers was approximately twice as high when the drug was delivered via Turbuhaler™ than via a pMDI (32% and 15% of the metered dose, respectively). Moreover, Turbuhaler™ deposited less drug in the mouth than pMDI, resulting in a more beneficial ratio of pulmonary to total systemic bioavailability (Fig. 2). In this study, deposition was calculated by two methods: from systemic availability (corrected for an assumed oral bioavailability of 13%) and using the charcoal block technique (in which activated charcoal suspension is used to adsorb swallowed drug, preventing its systemic absorption); similar results were obtained with each of the techniques (Table 2). The doubling in pulmonary deposition of budesonide with Turbuhaler™ compared with pMDI is consistent with in vitro fine particle results obtained using an Ander-

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Abbreviation: pMDI, pressurized metered-dose inhaler.
sen sampler fitted with an anatomical throat model. This finding suggests that in the case of budesonide, this in vitro technique may be a useful predictor of relative lung deposition.

There are significant differences between the deposition characteristics of various DPIs as well. For example, Thorsson et al. evaluated the pharmacokinetics of budesonide delivered by Turbuhaler vs. fluticasone delivered by a pMDI and by Diskus DPI in 13 healthy adult volunteers and eight adults with asthma. The delivery to the lung with the Turbuhaler was almost twice that of the pMDI and almost three times that of the Diskus (34%, 20%, and 13%, respectively). Similarly, in a group of children ages 8–14 years, the lung dose of budesonide via Turbuhaler was almost four times that of the fluticasone Diskus (30.8% vs. 8.0%). One cannot comment on the superiority of a drug-device combination based on lung deposition alone, but the effectiveness of topical therapy obviously depends on the medication being delivered to the airways target effectively.

The efficiency of a pMDI at delivering drug to the lung can be improved by using the pMDI in conjunction with a large-volume spacer or valved holding chamber. In healthy volunteers, lung deposition of budesonide from a pMDI plus Nebuhaler was estimated using pharmacokinetic methods to be 36% of the metered dose. One cannot comment on the superiority of a drug-device combination based on lung deposition alone, but the effectiveness of topical therapy obviously depends on the medication being delivered to the airways target effectively.

The efficiency of a pMDI at delivering drug to the lung can be improved by using the pMDI in conjunction with a large-volume spacer or valved holding chamber. In healthy volunteers, lung deposition of budesonide from a pMDI plus Nebuhaler was estimated using pharmacokinetic methods to be 36% of the metered dose. Similarly, in patients with asthma, the mean lung deposition, measured by scintigraphy, was 38% from pMDI plus Nebuhaler compared with 26% from Turbuhaler, and 12% from a pMDI alone (Fig. 3). Another study showed that the efficacy of a pMDI plus Nebuhaler used under ideal circumstances could indeed match the clinical efficacy of budesonide Turbuhaler. However, the high lung deposition of budesonide reported in these studies with a pMDI plus Nebuhaler does not appear to translate into superior clinical efficacy compared with Turbuhaler in routine practice (as explained in the subsequent sections). This may be related to problems in using pMDIs plus spacers correctly or to poor adherence in routine clinical practice, as opposed to the highly controlled environment in which clinical trials are performed. Alternatively, subjects may have already been on the plateau of the dose–response curve, so using a more efficient device may not have improved clinical outcome.

While some of the newer HFA-propellant pMDIs are formulated with the drug in suspension, most have the drug in solution, e.g. beclomethasone propionate, flunisolide, and ciclesonide. Beclomethasone has an MMAD close to 1 μm and an actuator deposition efficiency of about 50% in adults and greater than 30% in children. The fluticasone HFA formulation has a larger particle size to emulate the CFC preparation.

In children or adults who are unable to use a pMDI or DPI correctly, a jet nebulizer can be used to deliver therapeutic levels of any corticosteroid available as a nebulizing suspension (beclomethasone and budesonide) to the lungs. Dahlström et al. assessed lung deposition of budesonide by pharmacokinetic methods in adult volunteers from three different jet nebulizer systems—the PARI Inhalierboy, PARI LC Jet Plus, and Maxin MA-2. The MMAD for the Inhalierboy, Jet Plus, and MA-2 systems were 7, 5, and 3 μm, respectively. Relative to the nominal budesonide dose, lung
deposition was similar via the three nebulizers tested, ranging from 14% to 16%, despite the differences in particle size distributions. This emphasizes the fact that particle size is only one of the important variables in the assessment of aerosol delivery system performance. In this study, even though the PARI Inhalierboy® produced larger particles that are less likely to deposit in the lungs, it had a higher total output of drug than the other nebulizers which compensated for the particle size problem. The pharmacokinetics of budesonide nebulizing suspension have also been studied in asthmatic preschool children aged 3–6 years, using a PARI LC PLUS with a mouthpiece. Lung deposition as a per cent of inhaled dose was 18%, and the systemic bioavailability was 6%, which is about half that of adults.24 This indicates that the lower total lung dose in children is due to the increased fraction of the drug filtered out by the oropharynx (which does not add significantly to the systemic load) indicating the same doses can safely be used in children as adults.

Ultrasonic nebulizers are not well suited for suspensions, as demonstrated in several studies.25–27 For example, in one study the median inhaled mass of budesonide was approximately three-fold lower with an ultrasonic nebulizer compared with a jet nebulizer (10% of the nominal dose vs. 31%).28 For this reason, ultrasonic nebulizers are not recommended for use with budesonide nebulizing suspension.

Lung deposition and inhaled mass of nebulizer corticosteroids are also significantly influenced by the choice of patient–device interface, with use of a mouthpiece being shown to double lung deposition compared with use of a face mask.29 For example, one study of 158 children with asthma (ages 5–15 years) reported a mean inhaled mass of 5–7% of the nominal dose when budesonide was administered at a constant output using a jet nebulizer fitted with a unsealed face mask, compared with 9–12% when the same device was used at the same output but using a mouthpiece.29 Based on these data, the authors recommended that the use of non-sealing face masks with jet nebulizers should be avoided where possible. Mean inhaled mass could be further increased by switching the jet nebulizer from constant output to the breath-synchronized mode (an increase of up to 17–22% when used in conjunction with a mouthpiece).29 Despite the higher inhaled mass noted with the mouthpiece vs. the mask, a large clinical trial showed improvement in asthma symptom scores of similar magnitude between the two patient–device interfaces.30 In this study of infants and children aged 6 months to 8 years, the mask was used more in the younger children (mean 36.4 months) and the mouthpiece in older children (mean 70.0 months). The similar clinical effect between groups may be due to the smaller lungs and therefore a lower lung-dose requirement in the younger children.

Relationship between pulmonary deposition and therapeutic effect

The relationship between pulmonary deposition of inhaled β2-agonists and therapeutic effect is now well established,8,31,32 since the immediate effects of these agents on the airways are relatively easy to measure.8 As the pulmonary dose–response curve for the β2-agonists is sigmoidal (i.e. an initial slope followed by a plateau), increasing the dose deposited in the lung will elicit an increased therapeutic effect only if the initial dose was on the rising slope of the dose–response curve. The lack of measurable acute effects with ICSs makes it impossible to perform similar single-dose studies with these agents, although there are now a number of long-term studies suggesting that the relationship also holds true for corticosteroids.8,33,34 Therefore, for patients whose symptoms are not currently under control, switching from an ICSs device with a low pulmonary deposition to one with a high pulmonary deposition may prove advantageous. Conversely, for patients whose disease is well managed and who are using an ICSs device with a high pulmonary deposition, every effort should be made to reduce the dose to avoid unnecessary systemic side effects. The relationship between the site of drug deposition in the lung and therapeutic effect is, however, less well understood.8

Consistency of lung deposition

Dose reproducibility is an important consideration for ICSs therapy. In vitro assessments of device consistency appear to be poor predictors of lung-deposition consistency in vivo. For example, the fluticasone Diskus® inhaler has shown less variability in distribution of aerosol particle sizes than budesonide Turbuhaler® in in vitro simulations and, based on this, it has been argued that greater consistency in lung deposition could be expected with the Diskus® device.35,36 However, this has not been borne out in vivo; conversely, Turbuhaler® has shown less variability in lung deposition than the Diskus® inhaler in children and adults.18,37 Turbuhaler® was also found to provide greater consistency in terms of budesonide lung-deposition in vivo when compared with a pMDI, in spite of the fact that in vitro the variability in drug delivery was markedly less for the pMDI.14 This discrepancy
between in vitro and in vivo consistency may be due, in part, to a difference in aerosol particle size distributions between inhalers. Compared with the Diskus™ inhaler, Turbuhaler™ delivers 3–4 times as many fine particles, which may deposit more consistently and/or more peripherally in the intrapulmonary airways than larger particles. The difference between in vitro and in vivo results may, however, simply reflect the fact that the relatively small variability seen under standardized in vitro conditions becomes insignificant when biological and clinical factors (e.g. inhalation technique, airway geometry, and flow) are also considered.18,31

Lung deposition: misconceptions about effectiveness of devices

Dose delivery from DPIs such as Turbuhaler™ is reliant upon patients being able to generate an adequate peak inspiratory flow to disaggregate the drug into particles small enough to reach the lungs. For such devices, patients with large lung volumes generating high inspiratory flows are likely to attain high levels of drug deposition in the lungs. Some patients groups—notably asthmatic children and patients with advanced COPD—are often perceived as being unable to generate a sufficient inspiratory flow to achieve adequate clinical benefit from inhalation of medication via a DPI. However, a recent review of the literature7 has shown this to be a misconception.

Contrary to popular belief, patients with acute asthma are able to generate a high inspiratory flow through a DPI. The duration of the inspiratory flow, however, is shorter in this scenario due to a lower inspiratory volume. In this situation, a DPI is actually likely to perform better than a pMDI, particularly given the problems of coordinating actuation and inhalation during an acute asthma exacerbation.7 In one study of 99 adults presenting to hospital with acute exacerbations of asthma, 98% generated an inspiratory flow through Turbuhaler™ greater than 30 l/min, which is ideal for achieving an optimal clinical effect (only two patients recorded 26 l/min), the mean peak inspiratory flow being 60 l/min.36 Comparable findings have also been reported in studies in children with asthma39 and in patients with COPD.40 Indeed, in a study of 82 children with mild–moderate asthma, all children were capable of inhaling through a Turbuhaler™ at a flow rate > 40 l/min (mean values of 59 and 70 l/min for children aged 3–6 and 7–10 years, respectively).39 In children, there appears to be significant correlation between lung deposition of budesonide (delivered via Turbuhaler™, NebuChamber™ or nebulizer) and the size (diameter) of the mouth and oropharynx,41–43 while systemic exposure to the drug (i.e. lung deposition) was similar in small children and adults.42 This implies that from a safety perspective, the same doses can be used in children and adults without increasing the risk of systemic exposure. Importantly, the lower absolute lung deposition in children is offset by a higher orally deposited fraction, which does not contribute significantly to the total systemic load.

Clinical efficacy and safety of budesonide: influence of device

Clinical efficacy

Given the differences in inhalation characteristics and pulmonary deposition, it is not surprising that the various corticosteroid delivery systems also appear to have very different efficacy and safety profiles when administered to patients with asthma or COPD. The extensive clinical trial programme for budesonide has included all three major device types, and has demonstrated good efficacy for budesonide in the management of persistent asthma (irrespective of disease severity) in patients of all ages, as well as in the acute asthma setting and in patients with COPD.5

pMDIs are the most established means for ICSs delivery and have therefore been the benchmark against which new corticosteroid inhalation devices have been judged and against which dose selections for the new systems have been made. In the case of budesonide, results from early clinical studies comparing the efficacy of the same nominal dose of budesonide given via pMDI or via the Turbuhaler™ DPI showed a clear improvement in peak expiratory flow with the Turbuhaler™ compared with a pMDI.44–46 Subsequent randomized trials have calculated the difference in the dose:potency ratio of clinical efficacy between the two modes of administration to be approximately 2:1, indicating that when using Turbuhaler™ only half the nominal dose of budesonide needs to be given to achieve the same clinical efficacy as the full dose given via pMDI.21,47–49 For example, Agertoft and Pedersen21 compared the efficacy and safety of a pMDI and spacer device (Nebuhaler™) with Turbuhaler™ for the delivery of budesonide to children with chronic perennial asthma who were previously treated with budesonide via pMDI. Initially, 241 children with asthma had their dose of budesonide optimized during a run-in period. Once their asthma had stabilized, these children were then randomized to
receive budesonide at either the original dose via pMDI plus spacer or half the original dose delivered via Turbuhaler™. Compared with the pMDI plus spacer, Turbuhaler™ was found to be at least as effective in terms of peak expiratory flow measurements and was also associated with a reduction in β2-agonist use.

Agertoft and Pedersen33 also compared the efficacy of budesonide Turbuhaler™ and pMDI plus Nebuhaler in 216 children aged 6–14 years with chronic asthma who had received budesonide for 3–6 years. In this study, the budesonide dose was titrated down until optimal asthma control was reached. Although the mean dose of budesonide over the study period was significantly lower with Turbuhaler™ than with pMDI plus Nebuhaler (447 µg vs. 612 µg), children treated with Turbuhaler™ experienced significantly greater improvements in pulmonary function compared with those using the pMDI plus spacer (Fig. 4).

A 2:1 clinical potency ratio has also been demonstrated for budesonide via Turbuhaler™ relative to budesonide via pMDI without spacer in adults with asthma.47 In a general practice, study of 631 adults whose asthma was adequately controlled with inhaled budesonide or beclomethasone (200 or 400–500 µg twice daily, respectively) administered via pMDI, switching to half the daily dose of budesonide via Turbuhaler™ either once daily or in two divided doses was not associated with any loss in asthma control. Importantly, no significant differences were noted in peak expiratory flow, asthma symptom scores, bronchodilator use, or quality of life measures between those remaining on their usual treatment via pMDI and those switching to half-dose budesonide via Turbuhaler™. Based on these findings, attempts should be made to reduce the dose of budesonide when patients are switched from budesonide pMDIs to Turbuhaler™ treatment. The 2:1 clinical potency ratio for Turbuhaler™ relative to pMDI is consistent with the finding that budesonide lung deposition achieved with Turbuhaler™ is approximately twice that achieved with pMDI.14 Increased adherence and ease of use for Turbuhaler™ relative to pMDI might also contribute to these findings.50

Nebulization provides a useful alternative mode of delivery of corticosteroids that are available as a nebulizing suspension (beclomethasone and budesonide) in situations where a DPI or pMDI may not be suitable. Situations where budesonide inhalation suspension (Pulmicort Respules) would prove useful include:

- Children up to 5 years of age (approved up to 8 years of age in the US).
- Patients >5 years of age who experience difficulty using pMDIs or DPIs.
- Patients of any age who cannot coordinate or activate a pMDI or DPI because of dyspnoea.

In the case of budesonide, the clinical trial programme of the inhalation suspension has included infants and children up to 8 years of age with asthma severity ranging from mild to moderate. In this population, nebulized budesonide proved effective at daily doses of between 0.25 and 1 mg (administered as a single daily dose or in two divided doses) (Fig. 5)31,52 and has been found to be equally effective both in children <4 and ≥4 years of age.52 Shapiro et al.54 studied children ages 4–8 years with more severe asthma, who were already receiving ICSs at baseline. Doses up to 1 mg twice daily were effective at improving morning peak flow and reducing symptoms and need for rescue medication.54 Budesonide delivered via nebulization has been shown to be significantly more effective than placebo and sodium cromoglycate at improving symptoms and reducing asthma exacerbations in children with persistent asthma.55 In adults, high-dose budesonide (within the recommended dose range) via nebulization (synchronized with inhalation to minimize loss of drug) is more effective than budesonide delivered via pMDI plus spacer in managing severe persistent asthma, thus reducing the requirement for oral steroids and improving asthma symptoms and lung function (Fig. 6).35

![Figure 4](image_url) Mean daily dose of budesonide required for optimal asthma control and pulmonary function in children with asthma receiving budesonide via Turbuhaler™ or via a pMDI plus Nebuhaler for 3–6 years.23
Local side effects

Choice of inhalation device also has a significant impact on the nature and extent of side effects experienced with ICSs. Although systemic toxicities can occur at high doses of ICSs, in routine clinical practice it is the local side effects of these drugs—particularly hoarseness and oral candidiasis—that are the most frequent. Local side effects can be reduced by mouth rinsing after inhalation. Also, use of a valved holding chamber in conjunction with a pMDI reduces oropharyngeal deposition from approximately 80% of the metered dose to 10–15%. Since DPIs are used without spacers, there have been concerns that use of these devices may lead to increased local side effects. However, data from clinical studies with budesonide suggest the opposite to be the case. Selroos et al. monitored the incidence of local adverse events in 154 patients treated with budesonide or beclomethasone via pMDI plus spacer was 17% and 23%, respectively, decreasing to 6% (P < 0.001 vs. pMDI) when the patients were switched to budesonide Turbuhaler™ and followed for a further 2 years. The incidence of local adverse events (candidiasis, hoarseness, or sore throat or gums) in patients receiving budesonide or beclomethasone via a pMDI plus large-volume spacer (Nebuhaler® or Volumatic®, respectively) for 2 years, after which they were switched to budesonide Turbuhaler™ and followed for a further 2 years. The incidence of local adverse events (candidiasis, hoarseness, or sore throat or gums) in patients receiving budesonide or beclomethasone via a pMDI plus large-volume spacer (Nebuhaler® or Volumatic®, respectively) for 2 years, after which they were switched to budesonide Turbuhaler™ and followed for a further 2 years.
**Systemic side effects**

The systemic safety profile is an important consideration of any treatment used long term in the control of a chronic disease. If administered at high enough doses, all ICSs will produce clinically significant systemic activity. The systemic side effects of the available ICSs when used within the recommended dose ranges have been compared previously.\(^{57-66}\) Budesonide is the most thoroughly investigated ICSs in terms of long-term tolerability.\(^{3,61-65}\) Specifically, long-term use of budesonide is reported to have no adverse effect on final adult height of pediatric patients, bone mineral density, or ocular changes.\(^{3,62-65}\) and is the only ICSs assigned a Pregnancy Category B rating by the US Food and Drug Administration; all other ICSs remain at a Pregnancy Category C rating.

**Competence, adherence, and continuity**

The therapeutic effectiveness of any ICSs delivery device ultimately rests with the patient or caregiver, and in their ability to use the device correctly (competence) and as instructed by their physician (adherence). Indeed, it has been suggested that adherence is the major factor determining asthma control during long-term treatment.\(^{56}\)

Poor inhaler technique is a major problem for ICSs therapy, particularly for pMDIs that require coordination between actuation and inhalation. The cold Freon\(^{R}\) effect may also interrupt inhalation. Indeed, it has been estimated that as many as two-thirds of pMDI users and healthcare professionals teaching pMDI use do not perform the technique correctly.\(^{67,68}\) While poor technique results in inadequate doses of medication being administered, this can be substantially improved by good patient education. However, even following proper instruction, patients of all ages may be unable to use pMDIs efficiently.\(^{69,70}\) Use of a spacer or a valved holding chamber in conjunction with a pMDI can help coordinate actuation with inhalation and substantially reduce oropharyngeal deposition and the cold Freon\(^{R}\) effect.

For patients experiencing problems using a pMDI, a DPI such as Turbuhaler\(^{TM}\) might be a practical alternative. The generation of the aerosol from Turbuhaler is breath-initiated (eliminating the problem of coordinating inspiration with actuation), and the particle speed is equal to the velocity of the inspired air. This functional difference may explain why lung deposition is less variable when the drug is delivered via Turbuhaler\(^{TM}\) compared with delivery via a pMDI.\(^{71}\)

There are special considerations for optimizing aerosol delivery for infants and toddlers. Many young children fuss or cry when a mask from a nebulizer or holding chamber is applied to the face. However, crying significantly reduces the amount of aerosolized drug that reaches the lungs\(^{72-74}\) and increases dose-to-dose variability.\(^{75}\) To avoid crying, some caregivers will move the mask away from the face and give “blow-by” treatments. However, a poor face mask seal will result in 40–85% declines in inhaled dose with both MDI/spacer devices\(^{76,77}\) and nebulizers.\(^{78,79}\) Techniques that may overcome these problems include administering the aerosol during sleep,\(^{80}\) using an aerosol hood,\(^{81}\) or using blow-by with a tube or mouthpiece (rather than a mask) held within 4 cm of the child’s nose.\(^{82}\) Though no significant ocular problems have been reported in children taking usual doses of ICSs, care should be given to avoid direct drug exposure to the eyes of the child. New face masks are being designed to reduce eye exposure.\(^{83}\)

When selecting the optimal device for delivery of ICSs to an individual, patient preference should be a key consideration since it is one of the determinants of patient adherence to medication. Many causes of non-adherence with inhaled medication have been identified. Those relating to the device itself include low portability, impracticality, and difficulties in use. Also, reimbursement issues for durable medical equipment (spacers, nebulizers, and compressors) may play a significant role in the choice for many patients.

Budesonide is currently the only ICSs available for delivery via all three major types of devices for which in vivo lung deposition, pharmacokinetics and clinical efficacy have been investigated. This range of inhalation systems allows budesonide to be delivered effectively to patients of all ages and asthma severities. It allows the clinician and the patient to decide as a team which delivery system is best for them. Indeed, children with asthma may continue with the same drug as they mature; e.g. infants can be treated with Pulmicort Respules\(^{R}\) and later switched to budesonide Turbuhaler\(^{TM}\) at 5–6 years of age, if given appropriate training.\(^{62}\) This continuity of drug therapy throughout childhood and into adulthood helps the caregiver develop confidence in the drug.

**Conclusions**

ICSs are the cornerstone of therapy for patients with asthma and reduce exacerbations in patients...
Inhaled corticosteroids in the asthma and COPD

with COPD. Numerous studies have shown that in addition to improving lung function and asthma symptoms, ICSs significantly reduce the incidence of mortality and exacerbations requiring emergency physician visits, oral corticosteroid bursts, and hospitalizations. Indeed, ICSs therapy is now recommended as first-line therapy for all patients with persistent asthma. A range of delivery devices have been developed to cope with the different clinical circumstances and patient types receiving ICSs treatment. The clinical benefit of such therapy is determined by a complex interplay between the nature and extent of disease, the drug and its formulation, the characteristics of the device, and the patient’s ability to use the device correctly. An understanding of these factors is necessary when considering the most appropriate treatment option.

The corticosteroid, budesonide, is available for delivery via each of the three major types of inhalation devices, allowing physicians to select the optimal device for a particular patient, in addition to offering continuity in drug therapy as the child grows. When delivered by any of these devices, budesonide has been found to be effective in the treatment of persistent asthma irrespective of severity and age. Efficacy has also been demonstrated in patients with acute asthma and those with COPD. The ability to choose the appropriate aerosol delivery system for budesonide that matches the individual needs of the patient will help achieve successful treatment of obstructive airway diseases.

References


