Topical Review

Inhaled corticosteroids for adult asthma: impact of formulation and delivery device on relative pharmacokinetics, efficacy and safety

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Metered dose inhalers (MDIs) are the mainstay of inhaled steroid therapy for asthma. With the phasing out of traditional chlorofluorocarbon (CFC) propellants and their replacement with a new generation of CFC-free products, it is becoming clear that formulation and inhaler characteristics can markedly affect the drug delivery. It now seems necessary to compare inhalers not only on the basis of the properties of the steroid molecules but also to take into account the effect of propellants and other inhaler characteristics.

The impact of formulation and delivery device on relative pharmacokinetics, therapeutic efficacy and tolerability is illustrated by a new preparation of beclomethasone dipropionate (BDP) in an inhaler containing hydrofluoroalkane (HFA) propellant, called Qvar® (3M Health Care, U.K.). This drug preparation delivers the majority of particles (60%) in the fine particle range. This appears to be associated with improved lung deposition, a halving of dose requirements of BDP, but no evidence of clinically relevant adrenal suppression when used in therapeutic doses.

Prescribers need to be aware of the impact of formulation on pharmacokinetics of inhaled steroids in order to offer the lowest effective dose and give clear instructions to patients who are changing to a CFC-free product.

Introduction

International and national guidelines agree that inhaled steroids should be used regularly as first line therapy for all but very mild asthma (1–3).

Successful management of asthma depends on achieving adequate delivery of inhaled drug to the lung with minimum systemic glucocorticoid activity. Both the drug and the delivery device are therefore important in determining the efficacy and safety of inhaled steroids.

While metered dose inhalers (MDIs) remain the mainstay of inhaled steroid therapy, they have traditionally contained ozone-depleting chlorofluorocarbon (CFC) propellants. However, CFCs are now being phased out in agreement with the Montreal Protocol (4), necessitating reformulation of MDIs with non-CFC propellants, or a change to a different delivery system that does not rely on a propellant.

It is desirable that these developments in inhaler technology also improve delivery of inhaled steroids to the areas of lung affected by asthma. Airway inflammation is a cardinal feature of asthma. Bronchoscopic studies have demonstrated infiltration of the major airways with chronic inflammatory cells (5,6) and there is now increasing histopathological evidence for the presence of inflammation in the small airways (7–9). These latter pathological changes are in keeping with the well-recognized physiological changes associated with small airway narrowing in asthma.

The most widely used inhaled steroids in Europe are beclomethasone dipropionate (BDP), budesonide, and fluticasone monopropionate. In the past it was possible to compare these drugs on the basis of the properties of the steroid molecules. Now it is becoming clear that some of the new CFC-free formulations themselves can confer different properties which markedly affect the efficiency of delivery of the inhaled steroid.

This review addresses the pharmacokinetics, therapeutic efficacy and tolerability of BDP, budesonide and fluticasone in adults with asthma, with particular reference to Qvar, the new preparation of BDP in an inhaler containing hydrofluoroalkane (HFA) propellant instead of CFC, which has been developed in the U.K. by 3M Health Care. Studies in childhood asthma are not included.
Pharmacology and Pharmacokinetics

Corticosteroid receptors are found in most cell types and orally administered steroids therefore have widespread effects throughout the body (10). The objective of administering corticosteroids by inhalation is to improve the lung: systemic activity ratio compared with oral administration. High affinity for the corticosteroid receptor is essential for topical activity in the respiratory mucosa. While the activities of budesonide and fluticasone are due to the parent compounds, that of BDP is largely due to the active metabolite 17-beclomethasone monopropionate (17-BMP). Any potency comparison between these inhaled steroids must therefore take account of the biotransformation of BDP to 17-BMP in lung tissue or the gastro-intestinal tract (GIT). The affinities of the major inhaled steroids for the corticosteroid receptor are fluticasone > 17-BMP > budesonide > BDP (11–17).

Another important property of inhaled steroids is water solubility since this may facilitate dissolution of the steroid in the mucosal fluid, the ease of diffusion into and out of tissues, and anti-inflammatory potency (18). Lipophilicity is the converse of water solubility and this is linked to tissue half-life. Budesonide and 17-BMP are more water soluble and less lipophilic relative to BDP and fluticasone, and the half-life in tissue reflects these findings (Table 1) (11–17).

After inhalation, steroids can reach the systemic circulation via the lung or GIT (Fig. 1) (19,20). Rapid inactivation by hepatic biotransformation following systemic absorption is desirable to minimize systemic side effects, and the extent of first-pass inactivation in the liver is therefore important. All the major inhaled steroids have a high first-pass metabolism, with fluticasone being the highest at around 99% (15,21,22) (Fig. 1). Metabolic inactivation in the lung has not been demonstrated for any of the inhaled steroids currently available.

Delivery Systems

With the development of a new class of inhalers that utilize HFA propellants, it is important to compare their efficacy with current products which use either CFC propellants or deliver the drug via a dry powder device.

CFC-CONTAINING MDIs

With each actuation, traditional CFC-containing MDIs deliver a fixed quantity of drug in suspension. The importance of particle size for therapeutic response to inhaled drugs has long been recognized; fine particles (those with an aerodynamic diameter of less than 5 μm, often approaching 1 μm) are more likely to be deposited in the tracheobronchial and pulmonary regions of the lung, while larger particles impact on the oropharynx where they are retained or swallowed (23). Studies in asthmatic patients have shown the greatest pulmonary response to bronchodilators occurs with particles of less than 5 μm diameter, presumably as a result of increased airways deposition (24).

Lung deposition studies with bronchodilators show that typically only 4–20% of the delivered dose from a CFC-containing MDI reaches the lung, with around 80% of the dose deposited in the oropharynx (25–29). This figure assumes good inhaler technique but many patients with poor hand-breath coordination use MDIs suboptimally (30–32).

HFA-CONTAINING MDIs

A number of new CFC-free steroid products are under development by different pharmaceutical companies and it would appear, at least for the CFC-free BDP MDI, Qvar®, that lung deposition is different from that of CFC-containing preparations. Laboratory studies have used an Anderson Cascade Impactor (Anderson Instruments Inc., Smyrna, Georgia) to measure the size distribution of particles in an aerosol formulation and the resulting data are considered to reflect the likely outcome of human lung deposition studies (39). The aerosol is actuated into the impactor via an L-shaped tube or throat and passes through a series of plates with increasingly smaller pore size; those particles with a sufficiently large particle size will...
impact on the plate, while smaller particles pass on to the next stage. Smaller and smaller diameter particles are collected at each impaction stage. The Anderson Cascade Impactor has become a standard tool for assessing particle size distribution and is recognized by industry and regulatory authorities. Andersen Cascade Impactor data demonstrate that Qvar® delivers around 60% of the dose of BDP as particles in the fine particle range, mostly at the lower size range (mean 1.1 μm) (Fig. 2) (36,40). This compares with only 25% of the dose as particles in the fine particle range (3.5–4.0 μm) for CFC-BDP (Fig. 2). As expected, this increased proportion of fine particles has translated into improved lung deposition. 51% for Qvar compared with 4% for CFC-BDP in one study (36). Volunteers acted as their own controls and were trained to inhale reproducibly over a 3-s inspiration using a real-time breath pattern biofeedback device. Drug and technetium-99 radiolabel validation ensured that radiolabelling did not affect the particle size distribution. Following inhalation, deposition in lungs, abdomen, oropharynx and inhaler adapter, as well as the amount the subject expired through a filter trap, were determined by gamma scintigraphy. In addition to demonstrating increased lung deposition with the HFA-formulation, gamma camera imaging showed that BDP was deposited throughout the central, intermediate and peripheral airways with the HFA formulation whereas deposition was predominantly in the central airways with the CFC formulation (Fig. 3). An open study in patients with mild asthma has confirmed that Qvar® delivers most of the drug (56%) to the lung (36). The smaller particle size

**Fig. 1. Biotransformation of steroids after inhalation.**, 82% biotransformation to BMP within 5 min (20); †, more than 75% conversion to 17-BMP (19).

**Fig. 2. Particle size distribution of BDP in CFC suspension (----) and Qvar (-----) (Andersen Cascade Impactor Components).**
and improved lung deposition have been brought about by modifying the inhaler characteristics and replacing the conventional suspension of BDP in two CFC propellants and a surfactant, with a solution of BDP in HFA-134a. HFA-134a is an alternative non-CFC propellant, the safety of which has been extensively evaluated (41,42). This improved pattern of drug distribution is seen with or without the use of a spacer (AeroChamber®, Trude II, Ontario), as confirmed by a deposition study in healthy subjects using the methodology described above (43).

This altered deposition has implications for the pharmacokinetics of BDP. The pharmacokinetics of both single and multiple doses of Qvar have been compared with CFC-BDP (19). Both studies showed that half the dose of the HFA-based formulation gave similar serum drug concentration (using a novel beclomethasone assay procedure) to CFC-BDP. The maximum serum drug concentration and the area under the time concentration curve values for half the dose of the HFA formulation were similar to those with CFC-BDP.

With HFA-containing inhalers, deposition may be influenced by the physical interaction between the propellant and the particular drug. Thus particle size and deposition of salbutamol HFA-MDI is similar to that from a conventional CFC-containing MDI (35). The small particle size of Qvar® is in part due to the solution of BDP in HFA-134a but in addition the design of the inhaler valve and adapter, as well as the additive mixture used, will all influence particle size. It cannot therefore be assumed that the same particle size profile will apply to other CFC-free steroid MDIs currently under development by a number of pharmaceutical companies. Indeed, two recent product introductions (CFC-free BDP (Beclazone, Norton, Eire); CFC-free fluticasone (Flisolide, Glaxo-Wellcome, Germany)) have published dosing characteristics similar to the CFC-containing inhalers that they replace (44,45).

SPACERS AND BREATH-ACTUATED AEROSOLS

In patients with poor coordination, spacer devices used in combination with an MDI can help to improve the amount of drug received. Spacers form a reservoir from which patients can inhale the aerosol, allowing rapidly moving particles to slow down and larger particles to evaporate and reduce in size, thereby decreasing oropharyngeal deposition (46). However, delay between actuation and inhalation and the practice of multiple actuation before inhalation can have a major impact on the delivered dose (47,48). Furthermore, these devices can be bulky and cumbersome to use.

Breath-actuated aerosols offer an alternative approach to overcoming the problem of poor coordination because the release of a metered dose of drug is triggered by inspiration. Lung deposition studies using a breath-actuated Qvar® inhaler (Autohaler®, 3M Health Care, U.K.) have been performed in asthmatic patients (49). The device operated consistently over a wide range of inspiratory flows (26–137 l min⁻¹) and acted very early in the inspiratory cycle (0.2 s) (50), with delivery to the lungs of 56% of ex-actuator dose (49).

DRY POWDER INHALERS (DPIs)

DPIs offer a CFC-free preparation of inhaled steroids that overcomes the problem of poor hand-mouth coordination.
The drug is held as dry powder, either in a capsule which is perforated manually just before inhalation, or in a reservoir from which a dose is released manually just before inhalation. These devices are thus breath-dependent rather than breath-actuated devices and the medication delivery and fine particle mass of DPIs are dependent on the individual device and inspiratory flow rate of the patient, with optimal delivery of drug occurring at flow rates of 601 min⁻¹ (38,51).

Studies using a budesonide DPI (Pulmicort Turbuhaler®, Astra, Sweden) in healthy volunteers have suggested that lung deposition is approximately twice as great and dose consistency is less variable with DPIs than with budesonide CFC-MDIs (33,52), although this conclusion is not universally accepted and other studies have shown dose consistency to be more variable with DPIs (38,53).

NEBULIZERS

With nebulizers, even slow vital capacity inhalations have given good pulmonary deposition patterns (54) and hand-breath coordination is not required. However, there is no evidence that nebulizers are superior to hand-held inhalers or oral steroids (55) and their use is generally reserved for young or elderly patients who cannot cope with other devices (46). At the present time, budesonide is the only steroid available for administration by nebulizer.

Comparative Efficacy

National and international guidelines recommend a step-wise approach to the management of asthma (1–3). Standard-dose inhaled steroid therapy is generally regarded at 100–400 μg twice daily for BDP or budesonide and 50–200 μg twice daily for fluticasone. High-dose therapy is regarded as 800–2000 μg daily for budesonide or BDP and 400–1000 μg daily for fluticasone (3). The efficacy of standard-dose inhaled steroids was well documented as early as the 1970s. High-dose inhaled steroids offer clear benefits to certain patient groups although this has been more difficult to demonstrate, due in part to methodological difficulties in determining a dose-response relationship to inhaled steroids (56).

Clinical trials comparing the efficacy of BDP and budesonide in standard or high doses for the treatment of asthma generally show no clinically relevant differences between the two drugs. Over 20 such studies have been reviewed elsewhere (56–58). More recent comparisons (59–62) have employed different delivery devices, making it difficult to draw conclusions about the relative efficacy of the two steroid molecules. In these studies, there was some evidence that equal doses of BDP delivered by CFC-containing MDI were less effective than budesonide delivered by dry powder reservoir, arguing in favour of using budesonide delivered by a dry powder device. However, against this, a comparison of multiple dose-levels of BDP with multiple dose-levels of budesonide failed to show a dose-response for either drug, or any significant difference between drugs (63).

Studies comparing fluticasone with either BDP or budesonide in standard or high doses delivered by CFC-containing MDIs and dry powder devices have also been reviewed elsewhere (64–66). The majority of studies have compared a single dose-level of fluticasone with twice the dose of BDP or budesonide and have shown no differences between treatments when given by equivalent delivery systems, supporting the view that fluticasone is twice as effective as BDP or budesonide (67–72). In a meta-analysis of clinical studies comparing fluticasone and budesonide, fluticasone at half the budesonide dose resulted in a slightly greater improvement in morning peak expiratory flow and had less of an effect on cortisol (73). The efficacy ratio of 2.1 of fluticasone over BDP or budesonide has been more difficult to demonstrate in studies attempting to show a dose response to inhaled steroids (74,75).

Preliminary studies with Qvar® were carried out in small numbers of patients to establish its clinical efficacy at doses recommended for CFC-BDP (76). In a study by Dahl et al., 68 patients with asthma who were well controlled on CFC-BDP 200–600 μg day⁻¹ were included in a double-blind, two-period cross-over study (76). Patients were randomized to receive the same total daily dose of CFC-BDP or Qvar for 4 weeks. Measurements of asthma control (morning and evening peak expiratory flow, forced expiratory volume in 1 s [FEV₁] asthma symptom score, sleep disturbance or β-agonist use) showed statistically significant equivalence between CFC-free and CFC-based BDP (P=0.001). However, the patient population in this study was comparatively small and the study was not designed to establish equivalence. Therefore, having established that the new BDP formulation could benefit patients with asthma, subsequent parallel-group studies were carried out to establish the optimal dose of Qvar and to evaluate its efficacy and safety in a wide range of degrees of asthma severity and in different patient types.

In a dose-response comparison of CFC-BDP and Qvar®, a statistically significant dose-response relationship was demonstrated for both products over the range 100–800 μg (Qvar P=0.009, CFC-BDP P=0.003, for linear trend; Fig. 4) (78–81). Three hundred and twenty-three patients with moderately severe asthma were on a stable regimen of 400–1000 μg daily of inhaled corticosteroid with use of an inhaled β-agonist on an as-needed basis, and had a FEV₁ of 50–75% predicted. Lung function parameters (FEV₁, forced expiratory flow at mid-expiratory phase [FEF₂₅₋₇₅], morning peak expiratory flow [PEF] and per cent reversibility) were measured during a 7–14 day run-in period (inhaled steroid continued), during a 1–28 day single-blind inhaled steroid wash-out period (placebo inhaler used), and during 6 weeks of double-dummy, modified blind, randomized treatment (Qvar or CFC-BDP at 100, 400 or 800 μg daily).

In addition to confirming a dose-response relationship for BDP, this study also showed that higher doses of CFC-BDP than of Qvar were required to achieve the same improvement in FEV₁ (relative dose ratio of 2.6 [95% CI 1.1–11.6], Finney’s Parallel Line Bioassay method) and FEF₂₅₋₇₅ (relative dose ratio of 3.2 [95% CI 1.3–15.8], Finney’s Parallel Line Bioassay method). The novel design of this study overcomes many of the limitations of earlier.
FIG. 4. (a) Change from baseline at week 6 in FEV₁ as % of predicted value: CFC-BDP (——) suspension vs. Qvar® (---) (78-81) (⊙, 100 µg; □, 400 µg; Δ, 800 µg).
(b) At week 6 there was a statistically significant linear trend for increased improvement with increasing doses of both Qvar® (---) and CFC-BDP (——) [relative dose ratio 2.6 (95% CI 1.1-11.6)].

dose-response studies. Notably, steroid responsiveness was demonstrated following withdrawal of inhaled steroids in the run-in period, and patients were required to visit the clinic five times per week during the run-in, wash-out, and randomized treatment periods, to ensure proper MDI, PEF and spirometry technique.

Other studies support the finding of lower effective doses of Qvar® compared with CFC-BDP (82-84). In 347 patients with moderate to severe asthma, 100 µg Qvar was equivalent to 800 µg CFC-BDP (83), while in 233 patients with moderately severe asthma who were inadequately controlled on current inhalation therapy, 800 µg was equivalent to 1500 µg CFC-BDP (82). Both these studies employed double-blind, parallel group designs with 12 weeks on randomized therapy, and efficacy variables included morning and evening PEF, FEV₁, asthma symptoms and β-agonist use. In steroid-naive patients with mild to moderate symptomatic asthma, daily doses as low as 100 µg or 200 µg Qvar were significantly more effective than placebo in improving asthma control (85).

Tolerability and Adverse Effects

It should be stressed that, in general, inhaled steroids are remarkably safe. Of the few recognized side-effects, there is a low incidence of oral candidiasis. There is also the problem of hoarseness, probably related to laryngeal deposition and an associated steroid myopathy. One of the potential advantages of the HFA-BDP aerosol from 3M Health Care (Qvar) is that, because of the predominance of small particles, the majority of drug is delivered to the airways with reduced deposition in the throat. Early indications suggest that the incidence of local side-effects is low; in five multicentre clinical trials involving 740 patients on Qvar, throat swabs taken from patients reporting any oropharyngeal adverse event did not reveal any evidence of candidiasis. The incidence of dysphonia was comparable in both the Qvar® and CFC-BDP groups (3%) (86).

Oral corticosteroid therapy may give rise to systemic adverse effects associated with significant suppression of adrenal function. Bone loss and osteoporosis, skin thinning, and increased cataract formation have all been reported and decreased linear growth may be an issue in children. There is concern that these effects may also be seen with inhaled steroids, particularly when high doses are used long term.

EFFECTS ON HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) FUNCTION

Extensive clinical use of inhaled BDP and budesonide at doses less than 1000 µg daily, over the past 1-20 years, suggests that in adults, inhaled therapy with these agents is not associated with clinically relevant adrenal suppression. There has been much discussion over the preferred methods of evaluating the effect on hypothalamic-pituitary axis (HPA) function following the use of inhaled steroids. The different sensitivities of the variety of methods used do, to some extent, confound the interpretation of findings across the different inhaled steroids, as do the different inhaler devices used (18).

In general, dose-related suppression of the HPA axis has occurred with inhaled BDP or budesonide doses in excess of 1000 µg daily (66). For budesonide and fluticasone, which undergo 89 and 99% first pass hepatic metabolism respectively, lung bioavailability is the main determinant of systemic activity. For BDP, which has lower hepatic first pass extraction (79%) (19), gut bioavailability assumes greater importance (66). Thus, use of a spacer has been shown to decrease adrenal suppression caused by BDP (87).

The relatively low incidence of adrenal suppression with Qvar® in clinical studies is reassuring since it confounds the expectation that greater lung deposition (which results in more drug absorption from the lung) may adversely affect adrenal function. Morning plasma cortisol concentrations,
Table 2. Traditional corticosteroid inhalers available in the U.K.

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Device</th>
<th>Brand (manufacturer)</th>
<th>Strength (µg)</th>
<th>Propellant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>MDI</td>
<td>Beclazone (BN)</td>
<td>50, 100, 250</td>
<td>CFC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Becloforte (GW)</td>
<td>250</td>
<td>CFC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Becotide (GW)</td>
<td>50, 100, 200</td>
<td>CFC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Filair (3M)</td>
<td>50, 100, 250</td>
<td>CFC</td>
</tr>
<tr>
<td></td>
<td>MDI + integral</td>
<td>Becloforte Integra (GW)</td>
<td>250</td>
<td>CFC</td>
</tr>
<tr>
<td>compact spacer</td>
<td></td>
<td>Asmabec Spacehaler (Evans)</td>
<td>50, 100, 250</td>
<td>CFC</td>
</tr>
<tr>
<td>BA MDI</td>
<td>MDI</td>
<td>AeroBec Autohaler (3M)</td>
<td>50, 100, 250</td>
<td>CFC</td>
</tr>
<tr>
<td>BA MDI + integral compact spacer</td>
<td></td>
<td>Becotide Easi-Breathe (GW)</td>
<td>250</td>
<td>CFC</td>
</tr>
<tr>
<td>Single-dose DPI</td>
<td>MDI</td>
<td>Becotide Rotacaps and Rotahaler (GW)</td>
<td>100, 200, 400</td>
<td>None</td>
</tr>
<tr>
<td>Multiple-dose DPI</td>
<td>MDI</td>
<td>Becloforte Disks and Diskhaler (GW)</td>
<td>400</td>
<td>None</td>
</tr>
<tr>
<td>Budesonide</td>
<td>MDI</td>
<td>Pulmicort (AP)</td>
<td>50, 100, 250</td>
<td>CFC</td>
</tr>
<tr>
<td>Reservoir DPI</td>
<td></td>
<td>Pulmicort Turbuhaler (AP)</td>
<td>50, 100, 250</td>
<td>CFC</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>MDI</td>
<td>Flixotide (GW)</td>
<td>25, 50, 125, 250</td>
<td>CFC</td>
</tr>
<tr>
<td>Reservoir DPI</td>
<td></td>
<td>Flixotide Accuhaler (GW)</td>
<td>50, 100, 250</td>
<td>None</td>
</tr>
<tr>
<td>Multiple-dose DPI</td>
<td></td>
<td>Flixotide Disks and Diskhaler (GW)</td>
<td>50, 100, 250</td>
<td>None</td>
</tr>
</tbody>
</table>

MDI, metered dose inhaler; BN, Baker Norton; GW, Glaxo Wellcome; 3M, 3M Health Care; CFC, chlorofluorocarbon; BA, breath actuated; DPI, dry powder inhaler; AP, Astra Pharmaceuticals.

measured after 12 weeks of randomized treatment in two studies conducted for licensing purposes, support this assertion. In the first study (n=347) (83), cortisol levels were normal in over 96% of patients in each of three treatment groups (Qvar 400 µg daily, HFA placebo, CFC-BDP 800 µg daily). In the second study (n=233) (82), a direct comparison of Qvar 800 µg daily with CFC-BDP 1500 µg daily, significantly fewer Qvar patients than CFC-BDP patients had below normal morning plasma cortisol values (4.4% vs. 14.6%; P=0.024, Fisher’s exact test). In this study the two treatments were also comparable on all efficacy variables.

EFFECTS ON BONE TURNOVER

It cannot be assumed that systemic effects in various areas, e.g. adrenal function and bone turnover, will occur concurrently and to the same degree. For this reason, the effects on all relevant organ systems influenced by corticosteroids need be assessed separately. Measurement of markers of bone formation must be accompanied by measurement of markers of bone resorption, as the two processes are linked in the dynamic process of bone turnover.

In general, it is accepted that inhaled BDP and budesonide in dosages up to 800 µg daily are relatively free of effects on bone metabolism (66). However, this is based on a combination of short-term studies of biochemical markers of bone turnover and uncontrolled observations from clinical use over many years. There are currently insufficient data on HFA-BDP to make any worthwhile comparisons with other inhaled steroids. Two studies comparing fluticasone with budesonide have found the effects of the two drugs on markers of bone metabolism to be similar (75,88). There is considerable debate as to the clinical significance of short-term studies using biochemical markers. In some studies, reductions in serum osteocalcin (a marker of bone formation) were paralleled by reductions in bone density (89), while in others no correlation between the two measurements could be found (90). A review of nine published surveys of bone mineral density in patients receiving inhaled steroids has shown conflicting results (91).

It is often difficult to separate out the effects of high-dose inhaled steroids from the effects of previous oral corticosteroid exposure. A cross-sectional survey found that bone mineral density increased with increased cumulative inhaled steroids dose and vertebral fracture rate decreased with increased cumulative inhaled steroids dose (92). This may reflect bone repair following withdrawal from oral steroids. Prospective long-term monitoring of bone density and fracture incidence, in patients receiving long-term inhaled corticosteroids, may prove the only way to determine clinical risk.

OTHER SERIOUS ADVERSE EFFECTS

Increased cataract formation and diabetes mellitus may complicate treatment with oral corticosteroids but do not appear to be a problem with inhaled steroids, even in high doses (93).

Skin thinning and purpura have been associated with use of high-dose inhaled steroids (94). Easy bruising has been reported in patients on high-dose inhaled steroids, and the risk increased with age, dose and duration of use (95). Neutrophilic leucocytosis, eosinopenia and lymphopenia have been reported with high-dose inhaled steroids but to a
TABLE 3. HFA-corticosteroid inhalers recently introduced in Europe

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Device</th>
<th>Brand (manufacturer)</th>
<th>Strength (µg)</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>MDI</td>
<td>Beclazone CFC-free (BN)</td>
<td>50, 100, 250</td>
<td>Eire</td>
</tr>
<tr>
<td></td>
<td>BA MDI</td>
<td>Qvar® (3M)</td>
<td>50, 100</td>
<td>U.K.</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>MDI</td>
<td>Flixotide Evohaler (GW)</td>
<td>125, 250</td>
<td>Germany</td>
</tr>
</tbody>
</table>

MDI, metered dose inhaler; BN, Baker Norton; 3M, 3M Health Care; BA, breath actuated; GW, Glaxo Wellcome.

TABLE 4. Requirements for optimal inhaler use*

<table>
<thead>
<tr>
<th>Requirement</th>
<th>MDI</th>
<th>DPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CFC</td>
<td>Qvar®</td>
</tr>
<tr>
<td>Press &amp; Breath</td>
<td>Press &amp; Breath</td>
<td>Press &amp; Breath</td>
</tr>
<tr>
<td>Hand-breath coordination</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>High inspiratory flow rate</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Shake before use</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Prime after first use</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓ Mandatory; X, not required.
*Sources: Manufacturers' Patient Information Leaflets, MIMS Guides to asthma devices (103), and Ariyananda et al. (46).

TABLE 5. Transferring patients to Qvar® from a CFC-BDP or other steroid inhaler

<table>
<thead>
<tr>
<th>Daily dose of beclomethasone dipropionate (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFC-BDP inhaler</td>
</tr>
<tr>
<td>200–250</td>
</tr>
<tr>
<td>400–500</td>
</tr>
<tr>
<td>800–1000</td>
</tr>
<tr>
<td>1200–1500</td>
</tr>
<tr>
<td>1600–2000</td>
</tr>
<tr>
<td>Budesonide</td>
</tr>
<tr>
<td>200–250</td>
</tr>
<tr>
<td>400–500</td>
</tr>
<tr>
<td>800–1000</td>
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<td>Fluticasone</td>
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<tr>
<td>100</td>
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lesser extent than with oral therapy. They have not been associated with clinically significant adverse effects (96,97).

Effects of inhaled steroids on growth in children is a subject that has received much attention (98–100) but this is outside the remit of this paper, which is concerned only with asthma in adults.

Practical Aspects of Therapy

The implications of the introduction of a range of CFC-free inhaled steroids are not trivial. There are a number of different inhaled steroid products available in the U.K. (Table 2) and CFC-free steroids MDIs in Europe (Table 3). The important differences in the pharmacokinetics of these drugs will need to be considered when treating patients and addressing the traditional problems of offering the lowest effective dose, maximizing compliance (101,102) and overcoming poor inhaler technique (Table 4) (30,32,46,103). It is going to be vital that prescribers understand that one CFC-free steroid inhaler (Qvar®) can be used at half the traditional dose of CFC-BDP (44,45) or budesonide inhalers, and at the same total daily dose of fluticasone preparations (Table 5). We look to future editions of the British Thoracic Society guidelines to help clinicians take best advantage of the new range of CFC-free inhaled steroids.

Conclusions

Some patients may require high doses of inhaled steroid to control their asthma and individual titration is essential; the lowest maintenance dose that is consistent with efficacy
should be used to avoid dose-related effects on adrenal function and bone metabolism.

There is considerable variation between inhaler devices as to the amount of drug deposited in the lung and therefore contributing to therapeutic effect, and the amount deposited in the oropharynx and therefore contributing to unwanted systemic and local effects. These differences will be compounded as new products reach the market and it cannot be assumed that equal doses of the same drug from different inhalation devices will be bioequivalent.

While some CFC-free inhalers are likely to be therapeutically equivalent to the CFC-containing products they replace, others are not. There are now considerable data to indicate that the 3M Qvar® has reduced dose requirements to the amount of drug deposited in the lung and therefore contributing to therapeutic effect, and the amount deposited in the oropharynx and therefore contributing to the amount of drug deposited in the lung and therefore.

In the light of this, the U.K. Department of Health has recommended that Qvar should be prescribed only by brand name (104).

It is vital that prescribers and the entire health-care team are aware of these differences and give clear guidance to patients who are changing from a CFC-BDP MDI to Qvar, since stepping down the dose of inhaled steroid should be possible.

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