Safety of hydrofluoroalkane-134a beclomethasone dipropionate extrafine aerosol

P. J. THOMPSON*, R. J. DAVIES†, W. F. YOUNG‡, A. B. GROSMAN§ and D. DONNELL¶

*Asthma and Allergy Research Unit, Department of Medicine, University of Western Australia, Australia
†The London Chest Hospital, London, U.K.
‡Endocrine Testing Center, The Mayo Clinic, Rochester, MN, U.S.A.
§Department of Endocrinology, St. Bartholomew's Hospital, London, U.K.
¶3M Pharmaceuticals, Loughborough, Leicestershire, U.K.

Herein we assess the safety of an inhaled formulation of beclomethasone dipropionate (BDP) which uses the propellant hydrofluoroalkane-134a (HFA) for the treatment of asthma. Acute local tolerability (as assessed by the incidence of cough and mean forced expiratory volume after 1 s inhalation) was similar for both BDP and placebo formulated in either chlorofluorocarbon (CFC) or HFA propellants. A total of 43 patients were treated with HFA-BDP (0, 200, 400 or 800 µg day⁻¹) or CFC-BDP (800 µg day⁻¹) for 14 days and their 24 h urinary free cortisol (UFC) excretion and response to cosyntropin stimulation were measured. There was no difference in UFC between any of the doses of HFA-BDP and CFC-BDP. Adrenal responsiveness to cosyntropin stimulation was normal in all but one patient. Two large 12 week placebo-controlled HFA-placebo, HFA-BDP 400 µg day⁻¹ and CFC-BDP 800 µg day⁻¹ (n = 347), and HFA-BDP 800 µg day⁻¹ and CFC-BDP 1500 µg day⁻¹ (n = 233). For HFA-BDP at either dose, CFC BDP 800 µg day⁻¹ and HFA placebo, the number of patients with morning plasma cortisol concentrations below normal was less than 4.4% but was 16.6% for CFC-BDP 1500 µg day⁻¹. The incidence of adverse events was lower in the HFA-BDP groups than in the CFC-BDP groups (P = 0.012). The data indicate that, at doses of up to 800 µg day⁻¹, HFA-BDP is at least as well tolerated as CFC-BDP. Other studies have found that equivalent efficacy is reached at lower doses of HFA-BDP than CFC-BDP. Equivalent efficacy at a lower dose and equivalent safety at the same dose imply that HFA-BDP may have a more favourable risk:benefit ratio than CFC-BDP when used at the recommended lower doses.

Introduction

Inhaled corticosteroids are widely used as first-line preventative therapy in asthma (1) and are recommended as such in the Global Initiative for Asthma treatment guidelines (2), in the British Thoracic Society guidelines (3) and by the National Asthma Campaign in Australia (4). Various drugs are available, but beclomethasone dipropionate (BDP), which was among the first to be introduced, is still the most widely prescribed. It has been extensively used for the treatment of asthma for many years, and its safety profile within the recommended dose range is well established (5). The most common delivery device for administration of inhaled therapy is the metered dose inhaler (MDI), which uses a propellant to create a fine aerosol of suspended drug particles (6). Most MDI devices use chlorofluorocarbons (CFCs) as the propellant (6). However, CFCs are known to deplete stratospheric ozone (6), and the Montreal Protocol of 1987 has agreed to phase out their use (7).

Hydrofluoroalkane-134a (HFA) has been developed as a suitable alternative propellant. It contains no chlorine and therefore has no ozone-depleting potential, and it also has a significantly shorter life in the atmosphere than CFCs (8). It has been used to reformulate a number of inhaled asthma therapies;
however, this article concentrates on HFA–BDP extrafine aerosol (Qvar™, 3M Pharmaceuticals, St. Paul, MN, U.S.A.).

The safety of HFA, both as the propellant alone and in combination with various inhaled medications, has been extensively evaluated. HFA has been shown to be safe in animal toxicology studies (9, 10), in tolerance studies in healthy volunteers (11, 12) and in clinical trials in asthmatic patients (13). It has been approved for use in inhalers in more than 40 countries. Therefore, HFA, when used with BDP, itself is unlikely to generate any new safety issues.

However, lung deposition studies have found that the new formulation of BDP delivers more of the given drug to the airways and less to the throat (14). As a result, studies needed to be performed on the HFA BDP formulation to establish whether this altered delivery pattern could affect the frequency of the characteristic side-effects of inhaled corticosteroids. This report focuses on assessment of the hypothalamus–pituitary–adrenal (HPA) axis (5, 15), the acute topical safety of HFA–BDP (undertaken to assess any upper airway irritation) and the adverse events observed during the HFA–BDP clinical trial programme.

A reduction in the proportion of BDP impacting on the back of the throat should result in a lower incidence of local side-effects. An increase in the proportion delivered to the airways will increase the amount of drug delivered to the site of therapeutic action but may also result in increased systemic bioavailability and therefore, possibly, in an increased incidence of systemic side-effects.

Safety Parameters Measured

Adrenal function, which is an important indicator of systemic glucocorticoid effects (15), was assessed in two distinct types of studies. One of the more sensitive measures of adrenal function is 24 h urinary free cortisol (UFC) excretion (15). This, together with a stimulation test using an adrenocorticotrophic hormone (ACTH) analogue, was employed in a clinical pharmacology study. Here, the relatively small number of patients enabled verification of all doses and sample collection as they spent the entire study period within the clinic. In contrast, in the large clinical trials, use of such detailed measurements was impractical; the simpler but less sensitive measure of morning plasma cortisol concentration was therefore employed. Data from these two complementary types of studies are presented together in this paper, thus providing a detailed picture of the effects of HFA–BDP on adrenal function.

Acute tolerance was assessed in a cross-over study comparing the incidence of cough and mean forced expiratory volume after 1 s (FEV₁) after inhalation of CFC–BDP, CFC–placebo, HFA–BDP and HFA–placebo. Full details have been presented elsewhere (15).

Adverse events recorded in several large clinical studies are also presented in this paper.

Results

ACUTE TOPICAL SAFETY

A single-dose cross-over study in 18 patients compared the effects of high-dose HFA–BDP (200 µg), HFA–placebo, CFC–BDP (250 µg) and CFC–placebo on FEV₁. This study has been published in full elsewhere (16) but a detailed analysis of safety has not been presented. All the patients selected for this study were receiving maintenance treatment with budesonide administered from a breath-dependent dry-powder inhaler. This patient population was selected because patients routinely taking inhaled BDP may have already developed tolerance to any possible acute effects of BDP and may therefore not provide a fair assessment of the effect of the CFC formulation or the new HFA formulation.

Each patient received eight inhalations of the relevant medications on each of the four study days, representing twice the dose of propellant and drug likely to be taken at one time in routine practice. Cough counts were measured during and immediately following dosing, and FEV₁ was measured at 2, 10, 20, 40 and 60 min after dosing.

As shown in Fig. 1, there were no significant differences in the percentage change of FEV₁ from baseline between any of the groups at any time point. Cough counts also showed no statistically significant differences, although a trend towards higher cough counts...
was seen in the CFC groups. Thus, the acute topical effects of HFA propellant and HFA–BDP were at least as well tolerated as those of CFC propellant and CFC–BDP.

ADRENAL FUNCTION

The effects of HFA–BDP, CFC–BDP and HFA–placebo on adrenal function were investigated in a controlled clinical pharmacology study. The study population consisted of 43 patients, aged 18–65 years, with a clinical diagnosis of asthma of at least 3 months duration and who had not received corticosteroid therapy for at least 3 months before the study. All patients had an FEV\textsubscript{1} of at least 60% of predicted normal value and normal adrenal function before study entry. The patients were randomized into five parallel groups (HFA–placebo, HFA–BDP 200, 400 or 800 µg day\textsuperscript{-1} or CFC–BDP 800 µg day\textsuperscript{-1}) and received study medication for 14 days. Patients were aware of whether they were receiving CFC-based or HFA-based products, but both patients and physicians were blind to the dose of BDP received in the HFA-based inhalers. All patients stayed in the study clinic throughout the treatment period, ensuring optimal inhaler technique, 100% compliance with all medication doses and complete collection of samples. UFC and response to ACTH stimulation were used to assess adrenal function.

24 h Urinary Free Cortisol Excretion

Figure 2 presents the percentage change from baseline in 24 h UFC excretion after 14 days of treatment. There was a dose-dependent fall in 24 h UFC excretion with increasing doses of HFA–BDP. The mean percentage change in UFC excretion in patients receiving HFA–BDP at a dose of 200 µg day\textsuperscript{-1} did not significantly differ from that in the HFA–placebo group, whereas the mean percentage changes in UFC excretion in the groups receiving HFA–BDP 400 µg day\textsuperscript{-1} and 800 µg day\textsuperscript{-1} were significantly lower than in the placebo group. There was no statistically significant difference between the group receiving CFC–BDP 800 µg day\textsuperscript{-1} and the group receiving HFA–BDP 800 µg day\textsuperscript{-1}, although the median percentage excretion of 24 h UFC was slightly lower in the CFC–BDP group. Thus, at a dose of 800 µg day\textsuperscript{-1}, HFA–BDP caused no more adrenal suppression (as measured by 24 h UFC) than an equivalent dose of CFC–BDP used as the comparator is generally accepted as having non-significant clinical effects in adult patients (15).

Response to Adrenocorticotropic Hormone Stimulation

The response to ACTH stimulation was tested in all patients at study entry and after the 14 day treatment period. Plasma cortisol was measured before, and at 30 and 60 min after, injection of cosyntropin (a synthetic analogue of ACTH). A normal response was defined as meeting two of the following three criteria:

- normal pre-injection plasma cortisol (≥ 138 nmol l\textsuperscript{-1});
- normal incremental increase in plasma cortisol after injection (≥ 193-2 nmol l\textsuperscript{-1});
- normal peak plasma cortisol after injection (≥ 496·8 nmol l\textsuperscript{-1}).

Only one patient showed an abnormal response on two of the three parameters and therefore met the study criteria for an abnormal cosyntropin response. This single exception was a patient who commenced the study with a plasma cortisol level at the low end of
the normal range and, after treatment (with HFA-BDP 800 µg day⁻¹), showed a low baseline plasma cortisol level and a low peak value. However, her incremental response to cosyntropin was normal (≥ 193·2 nmol l⁻¹), indicating that adrenal responsiveness had not been lost.

**PLASMA CORTISOL**

Two large phase III studies included measures of morning plasma cortisol concentrations. Patients underwent a run-in period of 10–12 days before the study, to demonstrate a morning peak expiratory flow value of 50–85% of the predicted normal value. All patients then received a short course (7–13 days) of oral steroid treatment (equivalent to 30 mg day⁻¹ of prednisolone) and were then randomized to study treatment for 12 weeks. In one study (n = 347), patients were randomized to one of three treatments (HFA-placebo, HFA-BDP 400 µg day⁻¹ or CFC-BDP 800 µg day⁻¹), while the other (n = 233) comprised two treatment groups (HFA-BDP 800 µg day⁻¹ and CFC-BDP 1500 µg day⁻¹). At the end of the run-in period, plasma cortisol was determined in the morning (6.30-9.30 a.m. and 8-10 a.m. respectively). Subsequent measures, at the end of the oral steroid course and at the end of the 12 week study medication, were made within 30 min of the initial determination.

Figure 3 shows the percentage of patients in each treatment group with plasma cortisol below the lower limit of the normal reference range after 12 weeks of treatment.

![Figure 3](image)

**Fig. 3.** Percentage of patients with morning plasma cortisol below the normal range after 12 weeks treatment with HFA-BDP 400 or 800 µg day⁻¹, CFC-BDP 800 or 1500 µg day⁻¹, or HFA-placebo, compared with 7–13 days treatment with oral steroids: ■, below reference range after oral steroids; □, below reference range; △, above or within reference range.

Of those patients receiving the highest dose of BDP (CFC-BDP 1500 µg day⁻¹), 14 (14·6%) were below the lower limit of the normal range, compared with no more than four patients (4·4%) in any other treatment group. After oral steroid treatment, plasma cortisol levels were below the lower limit of normal in 42% of patients (Fig. 3), confirming the superior safety of inhaled corticosteroids over oral dosing. It should be noted that the cortisol assay employed had a cross-reactivity of about 25% with prednisolone. Prednisolone still present in the plasma after the oral steroid course may therefore have produced elevated readings in the cortisol assay, which could have masked low cortisol levels. It is therefore possible that the true percentage of patients with low plasma cortisol levels after the oral steroid course may have been even higher than shown in Fig. 3.

**ADVERSE EVENTS**

A total of 1429 patients have been enrolled in five large-scale phase III clinical trials. The overall incidence of adverse events, considered probably or possibly related to treatment, was lower in patients treated with HFA-BDP (11%) than in patients treated with CFC-BDP (16%; P=0.012) (Table 1). Most adverse events were mild to moderate in intensity, with severe adverse events reported by 3·8% of patients in the HFA-BDP group, 6·8% in the CFC-BDP group and 8·7% in the HFA-placebo group. The severe adverse events in the HFA-placebo group were mainly respiratory system disorders (5·5% compared with 1·7% in the HFA-BDP group and 1·3% in the CFC-BDP group), confirming the need for active steroid therapy.

The incidence of inhalation-route adverse events, whether related to corticosteroid presence or to propellant and excipients (e.g. dysphonia, cough, asthma symptoms) was lower with HFA-BDP (8%) than with CFC-BDP (12%; P=0.042) (Table 1).

The incidence of respiratory system disorders and, in particular, asthma-related adverse events was similar in patients taking HFA-BDP and patients taking CFC-BDP (Table 1). Not surprisingly, patients receiving HFA-placebo had a higher incidence of increased asthma symptoms (4%) than patients receiving either active treatment (<1% for both BDP groups).

Throat swabs were taken from all patients who had signs and symptoms indicating the possible presence of *Candida* infection. Oral candidiasis was diagnosed in one patient in the CFC-BDP group.

A review of adverse events relating to taste, including nausea, revealed that HFA-BDP does have a different taste to CFC-BDP, but that this taste is acceptable to most patients (17).
TABLE 1. Incidence of adverse events considered possibly or probably related to treatment in patients receiving HFA-BDP, CFC-BDP or HFA-placebo in large clinical trials [values are number of patients (%)]

<table>
<thead>
<tr>
<th></th>
<th>HFA-BDP (n = 740)</th>
<th>CFC-BDP (n = 400)</th>
<th>HFA-placebo (n = 289)</th>
<th>Overall P value</th>
<th>P value HFA vs CFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient with at least one adverse event</td>
<td>82 (11%)</td>
<td>65 (16%)</td>
<td>28 (10%)</td>
<td>0.012</td>
<td>0.012</td>
</tr>
<tr>
<td>All inhalation-route disorders</td>
<td>59 (8%)</td>
<td>47 (12%)</td>
<td>13 (4%)</td>
<td>0.003</td>
<td>0.042</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (&lt;1%)</td>
<td>6 (2%)</td>
<td>3 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphonia</td>
<td>22 (3%)</td>
<td>11 (3%)</td>
<td>4 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased asthma symptoms</td>
<td>1 (&lt;1%)</td>
<td>5 (1%)</td>
<td>1 (&lt;1%)</td>
<td>0.026</td>
<td>0.022</td>
</tr>
<tr>
<td>Site sensation</td>
<td>27 (4%)</td>
<td>23 (6%)</td>
<td>5 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taste sensation</td>
<td>13 (2%)</td>
<td>8 (2%)</td>
<td>2 (&lt;1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All respiratory system disorders</td>
<td>17 (2%)</td>
<td>7 (2%)</td>
<td>13 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughing</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased asthma symptoms</td>
<td>4 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
<td>11 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laryngitis</td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>11 (1%)</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The percentage of patients who withdrew from the studies was similar in both active treatment groups (8% for HFA-BDP and 10% for CFC-BDP) and lower than the percentage in the placebo group (21%). More patients in the placebo group withdrew because of inadequate response and worsening asthma, as might be expected from the lack of active prophylactic steroid treatment.

Discussion

The investigations reported here evaluated the safety of HFA-BDP for a range of parameters and in a variety of study designs. For all the parameters studied, HFA-BDP was shown to be at least as well tolerated as CFC-BDP on a µg for µg basis.

The study on acute topical safety in asthmatic patients found that HFA-BDP was no more likely to provoke cough or a fall in FEV₁ after inhalation than CFC-BDP, CFC-placebo or HFA-placebo. This is consistent with the excellent tolerability already demonstrated for HFA in animal and healthy volunteer studies (9–11) and in a clinical programme for HFA-salbutamol (13). It is also consistent with the adverse event data from the clinical trials presented here, showing that HFA-BDP appeared to be associated with a lower incidence of adverse events than CFC-BDP. This appears to confirm the expectation that the HFA-BDP reformulation would generate no new safety issues.

As described elsewhere (18) the HFA-BDP formulation produces an extraneous spray of droplets designed to improve delivery to the airways. Lung deposition studies (14) have confirmed that a higher dose of drug is delivered to the lungs and a lower proportion to the throat. As certain local side-effects commonly associated with the use of inhaled corticosteroids (e.g. dysphonia, candidiasis) are believed to be related to the presence of corticosteroid in the throat, HFA-BDP might be expected to exhibit a low incidence of these effects. The observation of a lower frequency of inhalation-route adverse events in the
clinical trials with HFA–BDP supports this possibility. Of particular importance is the fact that no patient treated with HFA–BDP displayed symptoms of candidiasis. This occurred even though spacers were not employed in the trials and patients were not instructed to rinse the mouth and throat routinely after dosing.

An increase in delivery of inhaled corticosteroids to the lung may lead to greater systemic availability of active glucocorticoids, as absorption via the lung reaches the systemic circulation directly, whereas absorption through the gut is subject to first-pass metabolism in the liver. The size of this effect differs with the absorption characteristics of each corticosteroid. For example, as fluticasone has little or no oral bioavailability (19), any improvement in delivery to the airways may cause a significant increase in systemic drug levels. This possibility was evaluated for HFA–BDP by investigating its effects on adrenal function, a marker of systemic glucocorticoid activity (5). Using UFC measurement (15), the excretion of UFC in patients treated with doses of HFA–BDP ranging from 200 to 800 μg day⁻¹ was not significantly different from that observed in the same study with CFC–BDP 800 μg day⁻¹. The degree of suppression of UFC observed in this study after administration of CFC–BDP was greater than that reported in other published studies (15). This is probably because the patients in the study were resident in the clinic throughout the treatment period, thus ensuring perfect compliance and good inhaler technique. Compliance with asthma medication is notoriously low (20–21), and many patients have poor inhaler technique (22–25). Thus, the patients in the present study almost certainly had a higher exposure to BDP than may be expected in routine practice. The observation of greater suppression of 24 h UFC excretion than may be expected following CFC–BDP treatment is consistent with this.

The same clinical pharmacology study also assessed the response to cosyntropin stimulation, an alternative measure of HPA axis function, and found that this was also normal in all but one subject. The single exception had low baseline and low post-treatment cortisol levels, which caused her to be classified as abnormal according to the study criteria. However, despite low absolute plasma cortisol, she displayed a normal incremental increase after cosyntropin stimulation, indicating that she retained intact adrenal responsiveness to exogenous corticotropin analogue administration. The clinical significance of this finding is uncertain.

Morning plasma cortisol concentration, a simpler but less sensitive measure of adrenal function, was assessed in two large phase III clinical studies. The number of patients with plasma cortisol concentrations below the lower limit of normal did not differ between the groups treated with HFA–placebo, HFA–BDP 400 or 800 μg day⁻¹, or CFC–BDP 800 μg day⁻¹, although there was a higher proportion in the group receiving CFC BDP 1500 μg day⁻¹. This observation is in agreement with published data. Adrenal suppression has been regarded as of negligible clinical importance in the routine management of most asthmatic patients on inhaled corticosteroid therapy (26) and, in adults, suppression of adrenal function is generally observed only at doses of CFC–BDP in excess of 1000 μg day⁻¹ (27, 28).

Thus, all three measures of HPA axis function found that HFA–BDP 800 μg day⁻¹ caused no more adrenal suppression than CFC–BDP 800 μg day⁻¹. The agreement between three different measures in studies of different design gives a high degree of confidence in this finding, indicating that the increased lung delivery of HFA–BDP is not associated with any greater incidence of HPA axis suppression at standard doses.

With the impending phase-out of all CFC-containing inhalers it is reassuring that the overall data support the safe switching of CFC–BDP patients to HFA–BDP. The adverse event profile of CFC–BDP is well characterized, and the low incidence of adverse events for HFA BDP compares favourably with CFC–BDP. These safety findings give confidence that the reformulation of BDP in the HFA propellant system has had no deleterious consequences.

Importantly, other studies have found that the HFA–BDP extrafine aerosol, with its ability to deliver a greater proportion of administered drug to the lung, is associated with greater anti-asthmatic effectiveness (29, 30). Equivalent efficacy has been demonstrated using a dose of HFA–BDP approximately half that of CFC–BDP (800 μg day⁻¹ compared with 1500 μg day⁻¹) (30).

With a lower dose providing equivalent efficacy, and equivalent safety at the same dose, the overall therapeutic ratio of the HFA–BDP formulation would appear to be substantially more favourable than that of the conventional CFC–BDP formulation. HFA–BDP appears to represent an advance in the treatment of asthma.

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