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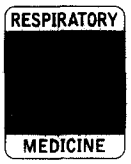

Inhaled beclomethasone (BDP) with non-CFC propellant (HFA 134a) is equivalent to BDP-CFC for the treatment of asthma

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As part of a development programme for a range of new CFC-free beclomethasone dipropionate (BDP) inhalers, two multicentre double-blind studies have been conducted to compare the therapeutic equivalence of a new HFA-134a propellant-formulated BDP metered-dose inhaler (Norton Healthcare Ltd, London, U.K.) with a CFC counterpart for the management of adult patients with all grades of asthma. Doses of 100 μg qds for 6 weeks were administered in a low dose study and in a high dose study 500 μg qds doses were given for 12 weeks.

Efficacy assessments included lung function (FEV_1) in the clinic and asthma symptoms, peak flow rates and bronchodilator use by patients on diary cards. Safety parameters measured included routine haematology and biochemistry (including serum cortisols), clinical adverse events and throat swabs for *Candida* spp.

Both CFC and HFA-formulations of inhaled BDP produced similar and significant improvements in lung function and asthma symptoms. In the low dose study, baseline to endpoint FEV_1 increased from $2{\cdot}2 \pm 0{\cdot}5$ l to $2{\cdot}5 \pm 0{\cdot}8$ l ($P=0{\cdot}0001$) with BDP-CFC and from $2{\cdot}2 \pm 0{\cdot}5$ l to $2{\cdot}6 \pm 0{\cdot}8$ l with BDP-HFA ($P=0{\cdot}0001$), with no significant differences between treatments. In the high dose study, corresponding increases were $2{\cdot}1 \pm 0{\cdot}7$ l to $2{\cdot}4 \pm 0{\cdot}9$ l ($P=0{\cdot}0002$) for BDP-CFC and $2{\cdot}1 \pm 0{\cdot}7$ l to $2{\cdot}3 \pm 0{\cdot}7$ l ($P=0{\cdot}017$) for BDP-HFA. PEF also improved similarly on both treatments in both studies. Both formulations were well tolerated with no difference in the pattern of adverse events, effect on serum cortisol or *Candida* colonization.

These studies showed that, in the management of asthma, the new HFA-formulated BDP metered dose inhaler is equivalent to, and directly substitutable for, the older CFC-formulated product at the same dose, making change-over for patients straightforward.

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Introduction

Beclomethasone dipropionate (BDP) is a well-established inhaled corticosteroid used for the prophylactic management of asthma. It is usually given via a pressurized metered dose inhaler (MDI). Currently most MDIs utilize a conventional chlorofluorocarbon (CFC) propellant to form the aerosol for inhalation. However, under the terms of the Montreal Protocol (1), use of CFCs is being phased out world-wide, including those used in medical devices, since these substances are implicated in damage to the earth's ozone layer. Recently, non-CFC propellants have been deployed which lack ozone-depleting potential. One of those to be used as a replacement propellant in medical inhalers is 1,1,1,2-tetrafluoroethane, otherwise known as HFA-134a. Extensive toxicological testing of HFA-134a has taken place under the auspices of the International Pharmaceutical Aerosol Consortium for Toxicology Testing (IPACT-1). Further clinical testing by pharmaceutical companies has shown this propellant to be free of any serious toxicity. In healthy man both single and multiple doses of HFA-134a are very well tolerated at dose levels above those likely to be used in therapeutic practice from inhalers (2–4). Furthermore, two salbutamol inhalers and two BDP inhalers containing HFA-134a are already licensed for the treatment of asthma in some countries (5,7–12). Although a 1:1 dose switch represents the most convenient and least confusing strategy for patients and doctors moving to the new CFC-free inhalers, a number of studies with one of the new BDP-HFA formulations have claimed efficacy at half the dose of the former CFC equivalent (7–9).

The present clinical studies in the treatment of moderate to severe asthma were planned to assess the therapeutic

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comparability of an alternative new formulation of BDP-HFA 134a in a MDI (Norton Healthcare Ltd, London, U.K.) with a conventional BDP-CFC MDI (Becotide® or Becloforte®, Allen & Hanbury's Ltd, U.K.). Prior in-house studies in healthy subjects with this new HFA formulation had shown that both single and multiple doses in the range of 50–250 μg were equally as well tolerated as those from the established BDP-CFC formulation.

Material and Methods

The research protocols comprised two multicentre studies: one to evaluate low dose BDP (50 μg shot^{-1}) and another to evaluate high-dose BDP (250 μg shot^{-1}) in both HFA and CFC formulations in standard MDIs. The clinical studies were conducted according to the principles of Good Clinical Research Practice in Europe (1991) and the Declaration of Helsinki (Hong Kong revision), as well as conforming to the guidelines set out by the Committee for Proprietary Medicinal Products on replacement of CFCs in metered dose inhalers (14). Both studies were approved by the local ethics committees of the centres concerned and by the respective national regulatory authorities.

STUDY SUBJECTS

Adult asthmatic patients (>12 years) of either sex, from general practice or hospital centres in the U.K., Eire and Poland, were eligible for the studies.

To satisfy inclusion criteria in both studies, patients needed to demonstrate a forced expiratory volume in 1 s (FEV_1) of 50–80% of predicted normal for their age, height and gender and a reversibility of 10% or more in FEV_1 following 200 μg of inhaled salbutamol.

All patients gave written, informed consent to participate in the studies.

Low dose study

Patients enrolled into the low dose study were currently receiving only inhaled bronchodilator therapy on an 'as required' basis, or inhaled sodium cromoglycate or nedocromil sodium. Those on oral corticosteroids, or who had been prescribed such agents in the previous 3 months, or who had taken more than three short courses of oral corticosteroids in the past year were excluded. Other exclusion criteria included concurrent systemic illness or recent hospital admission for asthma exacerbation, therapy for an upper respiratory tract infection, patients who were pregnant or nursing, and those with significantly abnormal laboratory screens. In addition, known or suspected hypersensitivity to the study medications, or those patients unlikely to be compliant with the study procedures also constituted grounds for exclusion.

High dose study

At baseline, patients in the high dose study were currently taking inhaled BDP-CFC at doses of 800–2000 μg daily via an MDI, otherwise inclusion and exclusion criteria were the same as for the low dose study.

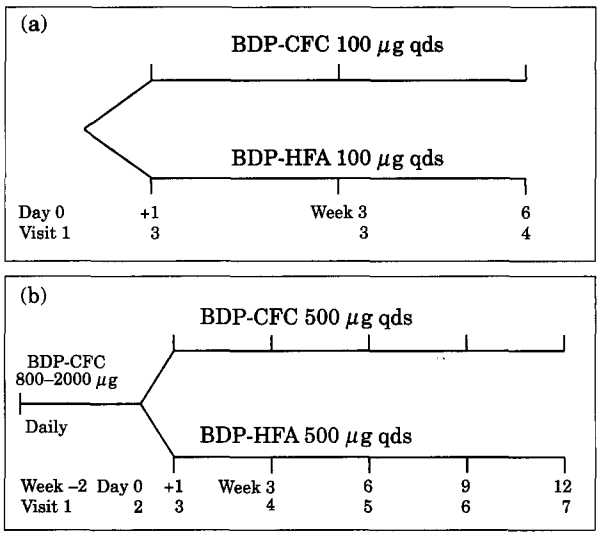

FIG. 1. Study schematics. (a) Low-dose study; (b) high-dose study.

STUDY DESIGN

Both studies were multicentre, double-blind and of randomized, parallel group design. The study schematics are shown in Fig. 1.

Low dose study

The low dose study compared BDP-HFA and BDP-CFC in doses of 100 μg four times daily (qds) for 6 weeks. Patients were seen in the clinic for assessment at the following times: at baseline, after 1 day of study treatment and after 3 and 6 weeks of treatment.

High dose study

Following a 2-week baseline period during which patients continued their usual asthma medication, the high dose study compared BDP-CFC and BDP-HFA in doses of 500 μg qds for 12 weeks. Patients were seen in the clinic at the start and end of the baseline period and after 3, 6, 9 and 12 weeks of study treatment.

The main variables assessed in both studies included lung function, asthma symptoms, vital signs, use of relief medication, adverse events, routine haematological and biochemical parameters (including 0900 h serum cortisols) and oropharyngeal examination plus throat swabs. Compliance was verified by reference to data on patient diary cards and inhaler technique was checked at each study visit.

METHODS

In both studies, following initial screening, eligible patients attended a baseline examination at the clinic, prior to which

TABLE 1. Assessments of asthma symptoms during the studies

Daytime symptoms	
Grade 0	No symptoms at all; unrestricted usual daily activities
Grade 1	Symptoms occurred, but with little or no discomfort; unrestricted usual daily activities
Grade 2	Symptoms occurred, were sometimes annoying or affecting usual daily activities (e.g. walking, dressing)
Grade 3	Symptoms severe; very little improvement after use of relief inhaler; not able to perform usual daily activities
Nocturnal symptoms	
Grade 0	Slept well; no asthma symptoms
Grade 1	Restless night, awakened because of asthma symptoms; may have used relief inhaler
Grade 2	Awakened more than once because of asthma symptoms; used relief inhaler
Grade 3	Awake all night because of asthma symptoms; used relief inhaler

they were asked to withhold their usual bronchodilator medication for a specified period. Lung function (FEV_1) was assessed by means of spirometry and asthma symptoms (cough, wheeze and bronchoconstriction) were graded according to a four-point disability scale (absence, mildly troublesome, troublesome, very troublesome). Vital signs including sitting blood pressure and heart rate were recorded. In addition, an oropharyngeal examination was made, with a throat swab for *Candida* spp. culture. A venous blood sample was taken for routine haematological and clinical chemistry parameters, including 0900 h serum cortisol.

Study medications were dispensed according to a randomization code and the patient instructed in their correct use. They were also given and shown how to use a mini-Wright peak flow meter to record twice daily peak flow measurements at home (best of three measurements on each occasion, morning and evening). Nocturnal and daytime asthma symptoms were recorded by the patients in daily diary cards, according to four point scales as above, as well as globally, characterizing the degree of interference with daytime activities and sleep (Table 1). The number of times that relief bronchodilator medication was used was also recorded by the patients.

At follow-up visits in the clinic, patients were assessed before taking their morning dose of study medication, having withheld any bronchodilator treatment for specified preceding intervals, depending on the particular drug. Asthma symptoms and vital signs were recorded as before and FEV_1 measured prior to, and 15 and 60 min after, the scheduled dose of study treatment. Patient diary cards were checked for completeness and any adverse events that had occurred in the intervening period were fully documented by the investigator. Blood tests (including 0900 h serum cortisol measurement) and oropharyngeal swabs were repeated at the final visit and additionally at 6 weeks in the high dose study. Throat swabs were also taken at intermediate visits if clinically warranted.

Any patient experiencing an exacerbation of asthma requiring systemic steroids or an increase in their inhaled steroid dose was to be withdrawn from the study. Those concurrently taking oral theophylline or inhaled anticholinergic therapy maintained the same dose throughout the study. Use of other research medications or intranasal, parenteral or depot injections of steroids was not permitted.

ANALYSIS

A therapeutically relevant difference between the two treatments in either study was regarded as a difference in mean pre-dose FEV_1 of >0·2 l. To detect this difference statistically, with a power of 90%, using 90% confidence intervals, a total of 100 evaluable patients was required in each study. To allow for drop-outs, target recruitment was set at 120 patients. Primary endpoint assessments were taken as the last available pre-dose FEV_1 values (mean of three readings) and treatment differences were compared using analysis of variance. Changes from baseline to endpoint FEV_1 were also calculated in each treatment group. Significance levels were regarded as $P<0·05$.

In addition, the proportions of patients with individual asthma symptoms (cough, wheeze and bronchoconstriction) were compared between treatments for each visit, as well as the symptomatic overall interference with daytime activities and sleep. Use of relief medication and PEF from diary card data were also compared between treatments. Adverse events were coded according to COSTART classification (6). Laboratory data and vital signs were compared at each visit with their baseline values.

All efficacy comparisons were performed both on an intention to treat and per protocol basis.

Results

EFFICACY

Results are expressed in terms of the intent-to-treat populations in each case although those for the per protocol populations were very similar.

TABLE 2. Patient demography (safety populations)

	Low-dose study		High-dose study	
	BDP-CFC (n=60)	BDP-HFA (n=59)	BDP-CFC (n=59)	BDP-HFA (n=60)
Age mean ± SD (years)	37·7 ± 18·3	39·7 ± 16·6	44·7 ± 13·3	43·0 ± 14·7
Range	13–72	13–80	16–77	16–80
M/F	34/26	33/26	29/30	25/35
Asthma history (years) mean ± SD	9·8 ± 8·5	11·4 ± 8·9	12·8 ± 11·1	11 ± 8·4
FEV_1 (% pred.) mean ± SD	67·6 ± 8·5	67·2 ± 8·8	70·1 ± 15·5	70·0 ± 15·2

TABLE 3. Lung function results (means ± SD) (intent-to-treat populations)

	Low-dose study		High-dose study	
	BDP-CFC (n=57)	BDP-HFA (n=56)	BDP-CFC (n=54)	BDP-HFA (n=54)
FEV_1 (l)				
Baseline	2·2 ± 0·5	2·2 ± 0·5	2·1 ± 0·7	2·1 ± 0·7
Endpoint	2·5 ± 0·8**	2·6 ± 0·8**	2·4 ± 0·9**	2·3 ± 0·7**
Between treatment difference (HFA-CFC)	0·1 n.s.		−0·1 n.s.	
90% CI for difference	−0·14, 0·35		−0·34, 0·5	
Morning PEF (l min^{-1})				
Baseline	391·5 ± 120·3	374·2 ± 113·3	353·6 ± 109·4	338·0 ± 100·8
Endpoint*	418·7 ± 118·5	412·9 ± 90·2	375·2 ± 107·7	364·3 ± 103·9
Between treatment difference (HFA-CFC)	−5·8 n.s.		−10·9 n.s.	
90% CI for difference	−15·7, 25·6		−36·1, 19·2	

*, Average for last 3 weeks of treatment; **, P=0·0001; n.s., not significant.

Low dose study

A total of 119 patients were recruited into the low dose study and formed the basis of the safety data population. Six patients (three in each group) were excluded from the efficacy evaluation for unverifiable data. Thus 113 patients comprised the intent-to-treat population, while 97 completed all visits as scheduled without protocol violations (per protocol population). Baseline patient demography, asthma severity and FEV_1 values were well matched at baseline for both groups (Table 2).

The primary efficacy variable (pre-dose FEV_1) showed a statistically significant increase in both BDP-CFC and BDP-HFA groups (P=0·0001) between baseline and endpoint after 6 weeks of treatment, these being of the order of 14–18%. FEV_1 increased from 2·2 ± 0·5 l to 2·5 ± 0·8 l with BDP-CFC and from 2·2 ± 0·5 l to 2·6 ± 0·8 l with BDP-HFA, with no significant differences between treatments (Table 3). Although more variable, morning PEF also increased similarly with both inhalers, such that the endpoint difference between treatments was only 5·8 l min^{-1} (<2%); results for evening PEF were similar.

With regard to asthma symptoms, approximately 80% of patients reported cough and 90% wheeze at study entry. After treatment, both BDP-HFA and BDP-CFC produced similar clinically relevant reductions of approximately 50% in the numbers of patients with these symptoms (Table 4). There was no overall difference in the use of relief medication by the two groups in either study, although few patients needed to use it.

High dose study

The total number of patients enrolled in the high dose study was 127, of which 19 were excluded from the efficacy analyses. Eight were withdrawn during baseline either for failure to satisfy entry criteria or adverse event, while another 11 patients had unverifiable data. Thus 108 patients formed the intent-to-treat population (92 per protocol population).

In this study both BDP-CFC and BDP-HFA were also associated with similar significant improvements in pre-dose FEV_1 from baseline to endpoint: from 2·1 ± 0·7 l to 2·4 ± 0·9 l (P=0·0002) for BDP-CFC and from 2·1 ± 0·7 l

TABLE 4. Proportion of patients with cough and wheeze (ITT population)

	BDP-CFC	BDP-HFA	*P*-value
Cough			
Low-dose study			
Baseline	46/57 (80·7%)	45/56 (80·3%)	0·963
Endpoint	22/48 (45·8%)	14/47 (29·8%)	0·109
High-dose study			
Baseline	44/54 (81·5%)	43/54 (79·6%)	0·81
Endpoint	23/47 (48·9%)	17/47 (36·2%)	0·21
Wheeze			
Low-dose study			
Baseline	53/57 (92·3%)	50/56 (89·3%)	0·491
Endpoint	19/48 (39·6%)	17/47 (36·2%)	0·733
High-dose study			
Baseline	49/54 (90·7%)	48/54 (88·9%)	0·75
Endpoint	22/47 (46·8%)	19/47 (40·4%)	0·53

to $2{\cdot}3 \pm 0{\cdot}71$ ($P=0{\cdot}017$) for BDP-HFA (Table 3). At the end of the study, there were no significant differences in either pre- or post-dose FEV_1 between treatments. Although increases in morning and evening PEF based on diary card data were also detected, baseline PEF values were not well matched between treatment groups. To increase precision an analysis of covariance, with correction for baseline, was performed. This showed similar responses in both parameters between treatments with no significant differences at endpoint.

Treatment-related reductions in the proportions of patients presenting with cough, wheeze or bronchoconstriction in the high dose study paralleled those of the low dose study, being similar for both groups (Table 4).

Thus, both studies showed that the improvements in lung function and asthma symptoms were similar for equivalent doses of BDP-CFC and BDP-HFA.

TOLERABILITY/SAFETY

A similar incidence and pattern of adverse events were reported by patients on both treatments in each study. The majority of these were mild or moderate in severity and did not result in treatment withdrawal. The most commonly reported adverse events are summarized in Table 5 and included candidiasis, infection, pharyngitis, cough, nausea and dyspepsia; there was no preponderance of any one type of adverse event in either group. The majority were not considered treatment-related by the reporting investigator. Although oral candidiasis comprised 20% of overall adverse events in the high-dose study, a quarter of these patients had this as a pre-existing condition. In 22 patients with throat swabs positive for *Candida albicans* at study entry, these resolved while under treatment, while 27 developed positive throat swabs at some stage during the study. Three patients in the low-dose study and five patients in the high-dose study were withdrawn due to a variety of non-serious adverse events.

Two patients (one in each study) experienced intercurrent exacerbations of asthma after 2 and 4 weeks in the study, resulting in their hospitalization and withdrawal from the study. These patients recovered fully after additional treatment. In the investigators' opinions, these were unlikely to be related to study treatment; one case was almost certainly due to bronchitis.

There were no clinically significant changes in vital signs or routine laboratory data in either study. No changes of note were recorded in serum cortisol in the low dose study. As to be expected, some patients had low cortisol values at some stage during the high dose study but the proportions of these were similar between treatments (31% *vs.* 36% patients on BDP-CFC and BDP-HFA, respectively). A number of values that were low at 6 weeks had returned to within the normal range at the end of 12 weeks of treatment in both groups. All patients were asymptomatic and none of the values was considered clinically significant by the investigators. Plots of those individual serum cortisol values in the high dose study exhibiting abnormalities at any stage or marked changes are shown in Fig. 2.

Discussion

The present two studies have demonstrated that for doses of 400 μg and 2000 μg daily, the newly formulated BDP-HFA metered dose inhaler is therapeutically equivalent to

TABLE 5. Incidence of most commonly reported adverse events [evaluable patients, *n* (%)]

	Low-dose study		High-dose study	
	BDP-CFC ($n=60$)	BDP-HFA ($n=59$)	BDP-CFC ($n=59$)	BDP-HFA ($n=60$)
Patients reporting any adverse event	36 (60%)	34 (58%)	51 (86%)	44 (73%)
Candidiasis	9 (15%)	7 (12%)	35 (59%)	28 (47%)
Infection	5 (8%)	6 (10%)	12 (20%)	6 (10%)
Pharyngitis	11 (18%)	6 (10%)	14 (24%)	9 (15%)
Cough	2 (3%)	3 (5%)	10 (17%)	3 (5%)
Nausea	3 (5%)	3 (5%)	3 (5%)	2 (3%)
Dyspepsia	4 (7%)	1 (2%)	—	—

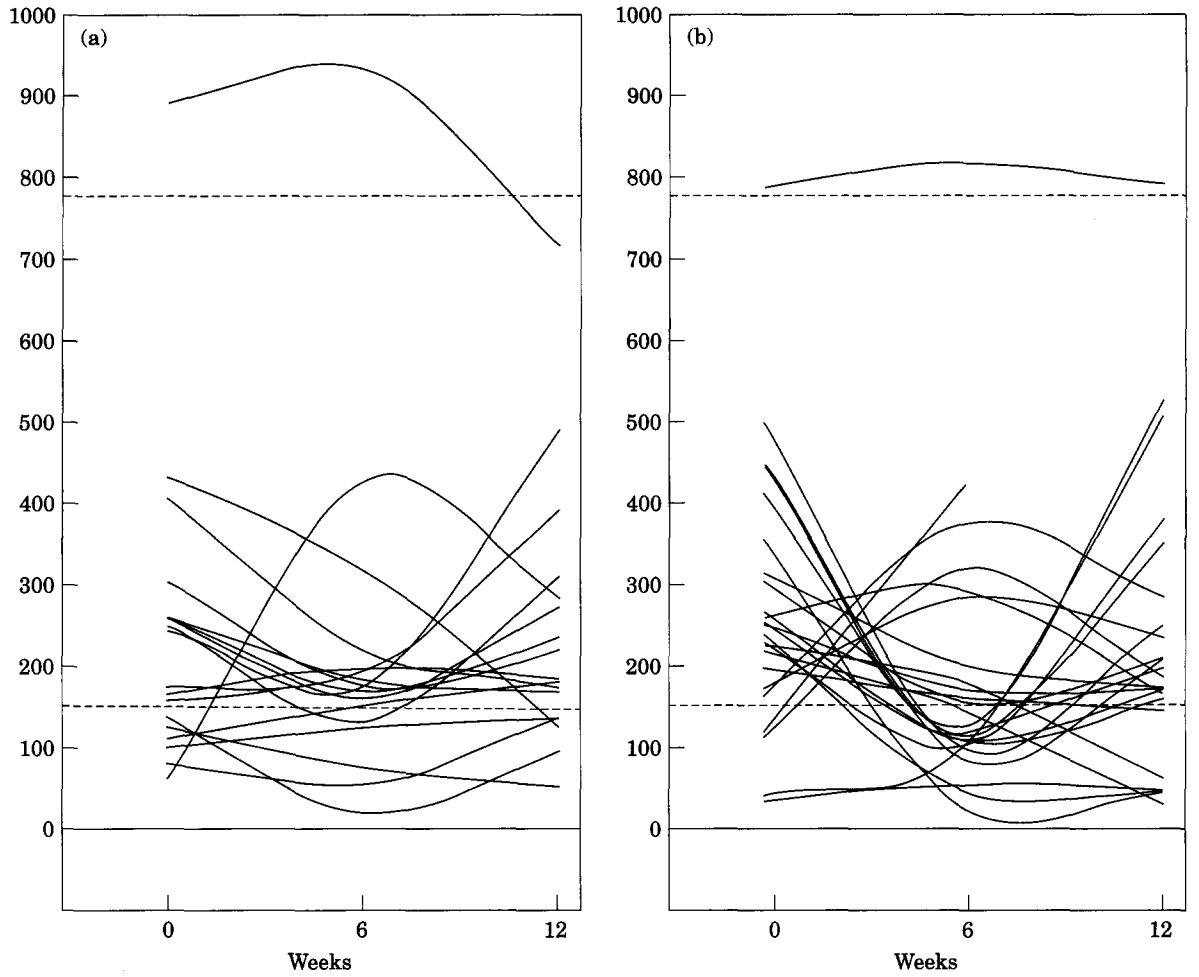

FIG. 2. Patients showing abnormal serum cortisol values during the high-dose study. (a) BDP-CFC; (b) BDP-HFA; normal range 165–172 nmol l^{-1}.

the currently established BDP-CFC product. No statistically or clinically significant differences were detected in terms of the patients' asthma control covering lung function, symptoms, relief medication usage or tolerability. Both products produced similar improvements in FEV_1 and PEF, with a progressive reduction in asthma symptoms throughout treatment. The BDP-HFA formulations were assessed in patients with both moderate and severe asthma who were characterized at entry as being sub-optimally controlled on their present therapy, as evidenced by their lung function data.

The higher incidence of minor adverse events recorded in the high dose study, such as candidiasis, pharyngitis and cough, may have been the result of not using spacer devices in this study. It is likely that these effects would be greatly reduced in normal practice by the use of a spacer or mouth rinsing after inhaler use, as is currently recommended practice.

Other recently published studies with another BDP inhaler formulated with HFA-134a (3M Pharmaceuticals, St Paul, MN, U.S.A.) have purported to show that it is possible to reduce the dose by half when switching patients from a BDP-CFC inhaler (7–9), on the basis of improved lung deposition with this formulation (10). However, clinical trials using both half-dose and full dose BDP-HFA against equivalent full dose BDP-CFC of these formulations, within the same study, are lacking. On a practical level, it is essential that any theoretical benefit of dose reduction when switching patients already stabilized on a BDP-CFC inhaler to a CFC-free version needs to be carefully balanced against the risks of loss of asthma control. Interestingly, another study using these same formulations has, in contrast, clearly shown that BDP-CFC and BDP-HFA are clinically and statistically equivalent on a 1:1 dose basis (11), a finding in keeping with the data found in the present studies.

The exact site of lung deposition for various asthma aerosols has not been verified. It is possible that much of the dose of BDP from a BDP-HFA inhaler may be absorbed systematically from the lung alveoli. This could in theory result in increased unwanted effects. Although the incidences of adverse events appeared similar in studies comparing doses of 800 μg BDP-HFA with 1500 μg BDP-CFC daily (53% and 59%, respectively) (8) it is unknown whether such incidences would be similar or not with equivalent doses of the two formulations. Further-

more, the similar or low incidence of morning serum cortisol values below normal range with this BDP-HFA formulation compared with its BDP-CFC counterpart in some studies may simply be a result of the lower doses of BDP-HFA used (8,12). The effects of higher identical daily doses (>1000 μg) of BDP-HFA and BDP-CFC were not ascertained in previously published work, but on the basis of the present studies would appear similar.

These studies presented here have demonstrated that patients may be switched directly from their existing CFC-formulated BDP aerosol to the new product formulated with HFA propellant at the same dose, without loss of asthma control or change in tolerability. Such considerations are important for patients and healthcare professionals in achieving a seamless transition to the new CFC-free asthma inhalers and are in keeping with current guidelines on asthma management (13).

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