ORIGINAL ARTICLE

Airway and systemic effects of hydrofluoroalkane fluticasone and beclomethasone in patients with asthma

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Background: With the transition to hydrofluoroalkane-134a propellants in metered dose inhalers, it is important to consider the efficacy and safety profiles of formulations containing inhaled corticosteroids. We examined the airway and systemic effects of hydrofluoroalkane-134a fluticasone propionate (FLU-HFA) and beclomethasone dipropionate (BEC-HFA) at recommended labelled doses.
Methods: Twenty mild to moderate asthmatics were randomised in crossover fashion to receive 6 weeks of 500 μg/day followed by 1000 μg/day FLU-HFA and BEC-HFA. Measurements were made at baseline after placebo run in and washout, and after each randomised treatment. The primary airway outcome for benefit was the dose of methacholine provoking a fall in forced expiratory volume in 1 second (FEV_1) of 20% or more (methacholine PD_{20}) and for systemic adverse effects was overnight urinary cortisol/creatinine (OUCC).
Results: For mean responses, both doses of BEC-HFA and FLU-HFA produced significant improvements in PD_{20} compared with baseline. The improvement was not significantly greater with 1000 μg/day FLU-HFA versus BEC-HFA, a 1.69 fold difference (95% CI 0.94 to 3.04). Both doses of BEC-HFA but not FLU-HFA caused significant suppression of OUCC compared with baseline, with significantly ($p<0.05$) lower values at 1000 μg/day for BEC-HFA versus FLU-HFA (1.97 fold difference (95% CI 1.28 to 3.02)).
Conclusion: There was no difference in the airway and systemic effects in patients with mild to moderate asthma between FLU-HFA and BEC-HFA at a dose of 500 μg/day. At 1000 μg/day there was increased systemic bioactivity with BEC-HFA compared with FLU-HFA, without any gain in airway efficacy.

M etered dose inhalers (MDIs) remain one of the most commonly used devices for delivering corticosteroids to the lung. In view of their ozone depleting potential, MDIs relying on chlorofluorocarbon (CFC) as the propellant are being phased out and the non-CFC propellant hydrofluoroalkane-134a (HFA) is an increasingly used alternative. Since current asthma management guidelines advocate the importance of early treatment with inhaled corticosteroids,[1] it is pertinent to consider the efficacy and safety profiles of such formulations.

The HFA-134a solution formulation of beclomethasone dipropionate (BEC-HFA; Beclazone CFC-free, Norton Healthcare, Ireland) has greater lung deposition than BEC-CFC.[2] This is in contrast to the HFA-134a suspension formulation of fluticasone propionate (FLU-HFA) which has similar lung deposition and anti-asthmatic efficacy to FLU-CFC.[3 4]

In a previous dose-response study in healthy volunteers there was significantly greater suppression of overnight urinary cortisol/creatinine (OUCC) with BEC-HFA than with FLU-HFA at the same labelled dose.[5] It may not be possible to extrapolate directly from healthy volunteers to asthmatic patients because reduced airway calibre in asthmatics has been shown to reduce the bioavailability of fluticasone propionate.[6–8] Moreover, studies in healthy volunteers do not produce information on anti-asthmatic efficacy.

We therefore carried out a study in mild to moderate asthmatics comparing the airway and systemic effects of FLU-HFA and BEC-HFA over the usual recommended daily dose range of 500–1000 μg for both products. We aimed to select doses which coincided with the steep part of the dose-response curves for both efficacy and systemic effects. Furthermore, we elected to use methacholine hyperresponsiveness as the primary outcome measure for airway efficacy, and suppression of OUCC as the primary outcome measure for systemic

adverse effects, as both are relatively sensitive measures for evaluating dose-response effects in patients with mild to moderate asthma.[9]

METHODS
Patients
Subjects with mild to moderately severe asthma were enrolled at random from our database of volunteers. Inclusion criteria included a forced expiratory volume in 1 second (FEV_1) of >70% predicted and a provocative dose of methacholine causing a 20% fall in FEV_1 (PD_{20}) of <500 μg. During the 3 month period before the screening visit patients were required to be using a short acting $β_2$ agonist only or maintained on a constant dose of inhaled corticosteroid up to 1200 μg/day, to have no history of respiratory tract infection and no oral corticosteroid use. All subjects gave written consent and the Tayside committee on medical research ethics gave approval for the study.

Study design
Patients were randomised into a single blind crossover study with 7–14 day placebo run in and washout periods. All inhaler canisters were masked, although placebo and active canisters were of a slightly different size, hence the term single blind. Investigators were unaware of the sequence of inhaled corticosteroid administration.

Subjects were given serial dosing for 3 weeks each of 250 μg twice daily followed by 500 μg twice daily FLU-HFA (Flixotide Evohaler, 250 μg per actuation, GlaxoSmithKline, Uxbridge, UK) and 250 μg twice daily followed by 500 μg twice daily BEC-HFA (Beclazone CFC-free, 250 μg per actuation, Norton Healthcare, Ireland) via a pressurised MDI. A run in and washout of 1–2 weeks using a placebo inhaler was used before

Table 1 Baseline data by treatment and sequence

	Baseline by treatment		Baseline by sequence	
	BEC-HFA	FLU-HFA	1st	2nd
Methacholine PD_{20} (µg)	97.0 (20.8)	96.2 (25.4)	80.8 (16.8)*	115.4 (30.4)
Exhaled NO (ppb)	11.3 (1.9)*	8.3 (1.3)	10.9 (2.0)	8.6 (1.2)
FEV_1 (% predicted)	87.9 (2.4)	89.1 (2.9)	87.9 (2.6)	89.1 (2.7)
Morning PEF (l/min)	437 (19)	445 (21)	440 (19)	442 (20)
OUCC (nmol/mmol)	7.08 (0.99)	6.14 (0.91)	6.91 (0.84)	6.07 (1.11)

BEC-HFA=HFA-134a solution formulation of beclomethasone dipropionate; FLU-HFA=HFA-134a suspension formulation of fluticasone propionate; PD_{20}=dose of methacholine provoking a fall in FEV_1 of 20% or more; NO=nitric oxide; FEV_1=forced expiratory volume in 1 second; PEF=peak expiratory flow; OUCC=overnight urinary cortisol/creatinine.
Values are means (SE) except methacholine PD_{20}, NO, and OUCC which are expressed as geometric means (SE).
*Denotes significant (p<0.05) difference between baseline values.

each randomised treatment. All subjects were required to have a second baseline PD_{20} at the end of the washout period within 1.5 doubling doses of the value after the run in. Following each washout and dosing periods—that is, on six mornings— patients attended the laboratory for exhaled tidal nitric oxide (NO) measurement, spirometric tests, and a methacholine bronchial challenge. Subjects also collected overnight urine (from 22.00 hours to 08.00 hours). A peak flow diary card was completed twice daily throughout the study.

Measurements
Spirometric tests were performed according to American Thoracic Society criteria[10] and end exhaled nitric oxide (NO) was measured using an integrated LR2000 clinical real-time NO gas analyser.[11] The methacholine bronchial challenges were performed using a standardised computer assisted dosimetric method in which cumulative doubling doses of 3.125–3200 µg were administered.[12]

Urine assays
All assays were performed in duplicate. Urinary creatinine was measured on a Cobas-bioautoanalyser (Sigma Pharmaceuticals plc, Watford, UK). Urinary cortisol samples were assayed with a radioimmunoassay kit (Diasorin Ltd, Wokingham, UK). There was no cross reactivity of the radioimmunoassay with fluticasone, beclomethasone, or any of their metabolites. The intra-assay and inter-assay coefficients of variation for creatinine were 3.5% and 4.3%, and for cortisol were 7% and 10.3%, respectively.

Statistical analysis
The study was powered at 80% to show a between treatment difference of 1 doubling dose of methacholine and a 20% difference in OUCC with a sample size of 16 patients. All data were analysed using Statgraphics software (STSC Software Publishing Group, Rockville, Maryland, USA). The NO, methacholine PD_{20}, and urine data were logarithmically transformed to normalise their distributions before analysis. An analysis of variance was performed using subjects, treatments, dose, and sequence as factors. This was followed by Bonferroni multiple range testing set at 95% confidence intervals (two tailed, p<0.05). All comparisons were considered significant at p<0.05 in order not to confound the overall alpha error. Comparisons were made with the pooled baseline values— that is, mean baseline values after placebo run in and washout—for effects within and between treatments.

RESULTS
Thirty subjects were enrolled and 20 (eight men) completed the study. Of those who dropped out, two had an exacerbation in the placebo run in period, two withdrew for personal reasons in the first randomised treatment, and six were not

methacholine responsive after the placebo run in. The mean (SE) age of those completing the study was 38 (4) years. The mean (SE) daily inhaled corticosteroid dose was 485 (78) µg. Ten patients were taking beclomethasone dipropionate, two were taking budesonide, and one fluticasone; the others used a short acting β_2 agonist only on an as-required basis.

At the initial screening visit before the run in the mean (SE) FEV_1 was 2.93 (0.19) l (93 (2)% predicted) and mean (SE) mid forced expiratory flow (FEF_{25-75}) was 2.61 (0.20) l (66 (4)% predicted). The mean end tidal NO was 8.3 (1.4) parts per billion and geometric mean methacholine PD_{20} was 84 (18) µg.

Baseline values after the run in and washout periods were compared by treatment and sequence; a significant (p<0.05) difference in methacholine PD_{20} was found for comparison by sequence (difference 1.43 fold (95% CI 1.11 to 1.83), table 1).
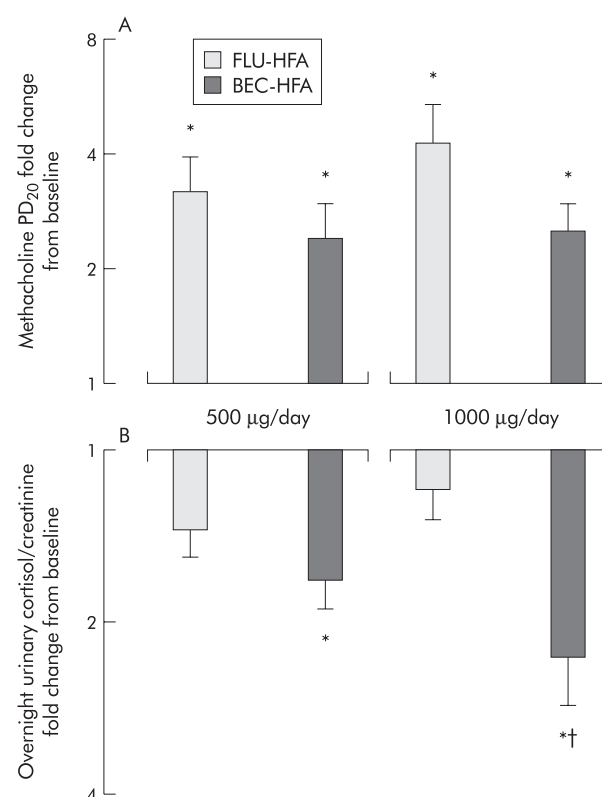

Figure 1 Fold change from baseline for (A) methacholine PD_{20} and (B) overnight urinary cortisol/creatinine (OUCC) with 500 µg and 1000 µg doses of hydrofluoroalkane-134a fluticasone propionate (FLU-HFA) and hydrofluoroalkane-134a beclomethasone dipropionate (BEC-HFA). *p<0.05 v baseline; †p<0.05 FLU-HFA v BEC-HFA 1000 µg/day.

Table 2 Airway and systemic data

	Pooled baseline	FLU-HFA (500 µg/day)	FLU-HFA (1000 µg/day)	BEC-HFA (500 µg/day)	BEC-HFA (1000 µg/day)
Airway data					
Methacholine PD_{20} (µg)	96.6 (22.1)	308.3 (93.2)*	416.0 (145.7)*	234.1 (72.9)*	245.9 (71.0)*
Exhaled tidal NO (ppb)	9.7 (1.5)	4.8 (0.8)*	4.9 (0.7)*	4.9 (0.6)*	5.0 (1.1)*
FEV_1 (% predicted)	88.5 (2.5)	92.8 (2.4)*	91.9 (2.4)*	92.8 (2.3)*	93.0 (2.2)*
Morning PEF (l/min)	443 (19)	455 (20)*	457 (20)*	455 (21)*	461 (20)*
Systemic data					
OUCC (nmol/mmol)	6.59 (0.70)	4.78 (0.62)	5.62 (0.98)	3.91 (0.58)*	2.86 (0.60)*†

BEC-HFA=HFA-134a solution formulation of beclomethasone dipropionate; FLU-HFA=HFA-134a suspension formulation of fluticasone propionate; PD_{20}=dose of methacholine provoking a fall in FEV_1 of 20% or more; NO=nitric oxide; FEV_1=forced expiratory volume in 1 second; PEF=peak expiratory flow; OUCC=overnight urinary cortisol/creatinine.
Values are expressed as means (SE) except methacholine PD_{20}, nitric oxide and urine data which are expressed as geometric means (SE).
*Denotes significant (p<0.05) difference from pooled baseline; † denotes significant (p<0.05) difference between FLU-HFA and BEC-HFA at 1000 µg/day dose.

Table 3 Airway and systemic differences between corticosteroids

	500 µg/day FLU-HFA v BEC-HFA	1000 µg/day FLU-HFA v BEC-HFA
Methacholine PD_{20}	1.32 (0.71 to 2.45)	1.69 (0.94 to 3.04)
Overnight urinary cortisol/creatinine	1.22 (0.87 to 1.72)	1.97 (1.28 to 3.02)

Values for primary outcome variables are shown as geometric mean fold differences (95% CI) between FLU-HFA and BEC-HFA. 95% CI which exclude unity indicate a significant (p<0.05) difference.

Methacholine challenge

Both doses of FLU-HFA and BEC-HFA showed significant improvements (p<0.05) in geometric mean methacholine PD_{20} compared with baseline. At 1000 µg/day the improvement with FLU-HFA was not significantly greater than with BEC-HFA (mean difference 1.69 fold (fig 1, tables 2 and 3). There were also no significant differences in randomised treatment effects when analysed according to sequence, in terms of being given first or second.

Other efficacy parameters

Both doses of FLU-HFA and BEC-HFA caused significant improvements in FEV_1 percentage predicted, morning peak flow, and NO compared with baseline. There were no significant differences between treatments at either dose (tables 2 and 3).

Urinary cortisol/creatinine excretion

The OUCC was significantly suppressed compared with baseline with both doses of BEC-HFA but not FLU-HFA; at the 1000 µg/day dose there was significantly (p<0.05) greater suppression with BEC-HFA than with FLU-HFA, amounting to a 1.97 fold mean difference (fig 1, tables 2 and 3). Individual OUCC data and geometric means are shown in fig 2. There were no significant differences in treatment response when analysed according to sequence.

DISCUSSION

Our results for mean data on airway efficacy showed that both doses of BEC-HFA and FLU-HFA significantly improved the methacholine PD_{20} compared with baseline. The mean improvement at 1000 µg/day was 1.7 fold greater with FLU-HFA than BEC-HFA which was non-significant, as denoted by the 95% CI which included unity. For mean data on systemic adverse effects, significant suppression of OUCC occurred with both doses of BEC-HFA compared with baseline but not with FLU-HFA; the suppression at 1000 µg/day was 2.0 fold significantly greater with BEC-HFA. Thus, there was no difference in the airway or systemic effects between FLU-HFA and BEC-HFA at the lower dose in patients with mild to moderate asthma. At the higher dose there was an increased systemic bioactivity with BEC-HFA compared with FLU-HFA, without any gain in airway efficacy. This suggests a deteriorating airway-systemic ratio with BEC-HFA at the higher dose.

We acknowledge that our patients had relatively well preserved mean values for FEV_1 % predicted (93%), although this was not the case with FEF_{25-75} % predicted (66%). As FEF_{25-75} is a better index of small airway calibre than FEV_1, the propensity for alveolar systemic absorption would be expected to be reduced in our patients compared with healthy subjects. We would therefore expect to see much lower lung bioavailability in patients with more severe asthma (FEV_1 <60% predicted), although this would have precluded performing a methacholine challenge for safety reasons.

Although our patients had relatively normal FEV_1 values, they had severe airway hyperresponsiveness in terms of their screening methacholine PD_{20} of 84 µg (equivalent to a PC_{20} value of 0.8 mg/ml). We therefore felt there was plenty room for improvement, given that the highest dose of methacholine was 3200 µg. However, as there was no further significant improvement in methacholine response above 500 µg/day of either corticosteroid, it is likely that we missed the steep part
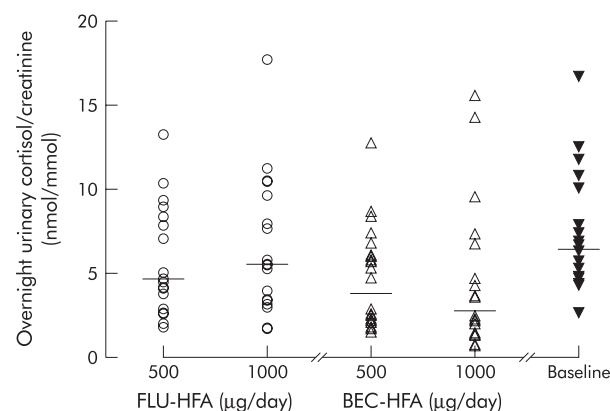

Figure 2 Individual data for absolute values of overnight urinary cortisol/creatinine (OUCC) for hydrofluoroalkane-134a fluticasone propionate (FLU-HFA, open circles), hydrofluoroalkane-134a beclomethasone dipropionate (BEC-HFA, open triangles), and baseline (filled triangles) with geometric means indicated by horizontal bars.

of the dose-response curve. In designing a dose-response study to evaluate both airway and systemic effects, there is always a compromise in dose selection in terms of achieving the steep part of the curve for both end points. One could argue, however, that the higher dose is less relevant for treating mild to moderate asthma. In more severe asthma with reduced lung bioavailability resulting from decreased airway calibre, it is likely that the difference in OUCC seen at 1000 µg/day would be attenuated.

There are some methodological points to discuss. The choice of methacholine PD_{20} was based on data which have shown a dose-response relationship for this end point in short to medium term studies with inhaled corticosteroids.[13 14] This is in contrast to lung function which shows a much flatter dose-response with fluticasone propionate and other corticosteroids.[15–17] Although we found a significant 1.43 fold significant difference in methacholine PD_{20} between baseline values by sequence, this was less than the twofold difference on which the study was powered. It is difficult to separate out the real effects of time and dose on methacholine PD_{20}, although the effects on OUCC occur more rapidly and reflect the pharmacokinetics for reaching steady state plasma levels. We have previously shown no difference in the effects of inhaled corticosteroids on methacholine PD_{20} when evaluated at 2 and 4 weeks, although it is conceivable that small further improvements may occur after several months.[18]

We chose OUCC as the primary systemic end point as this is a sensitive measure of basal hypothalamic-pituitary-adrenal axis (HPA) axis activity and is as sensitive as an integrated 24 hour plasma or urine cortisol profile.[19 20] What is the potential clinical relevance of the adrenal suppression observed in our study? We only measured OUCC as an index of basal HPA axis activity. The greater suppression of OUCC with BEC-HFA might in turn translate into a greater propensity for impaired adrenal reserve as measured by dynamic stimulation with low dose Cosyntropin or corticotropin releasing factor.[13 21]

One of the potential therapeutic benefits of the extra fine BEC-HFA solution formulation is the ability to reach the smaller airways with particles <2 µm in diameter. A limitation of our study was therefore that we did not include any measure of small airways response. It is also worth noting that we used a formulation of BEC-HFA which, like FLU-HFA, is licensed for use up to a maximum recommended labelled daily dose of 2000 µg, hence the rationale for comparing both drugs on a µg equivalent basis. Our data for OUCC in asthmatic subjects at 1000 µg/day showed a 2.0 fold greater suppression with BEC-HFA than with FLU-HFA, while in healthy volunteers there was a 1.64 fold difference at the same labelled dose with the same formulations.[5] These observations are perhaps not surprising as the BEC-HFA formulation exhibits 1.9 fold greater lung bioavailability and 2.3 fold greater cortisol suppression than the same labelled dose of the BEC-CFC formulation.[2 22] Furthermore, the FLU-CFC formulation exhibits 1.5 fold greater lung bioavailability and 1.9 fold greater cortisol suppression than the FLU-HFA formulation.[23 24]

In summary, our study showed no difference in airway or systemic effects with BEC-HFA and FLU-HFA at 500 µg/day in patients with mild to moderate asthma. With a dose of 1000 µg/day there was greater systemic bioactivity with BEC-HFA than with FLU-HFA, with no gain in airway efficacy. Further dose ranging studies are required with HFA formulations in more severe asthmatics to characterise the long term effects on end points such as exacerbations, small airway function, dynamic HPA axis measures, and bone density.

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