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

G P Currie, S J Fowler, A M Wilson, E J Sims, L C Orr, B J Lipworth

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 (FEV1) of 20% or more (methacholine PD20), 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 PD20 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 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.

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 (FEV1) of >70% predicted and a provocative dose of methacholine causing a 20% fall in FEV1 (PD20) of <500 µg. During the 3 month period before the screening visit patients were required to be using a short acting β2 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...
Spirometric tests were performed according to American Thoracic Society criteria and end exhaled nitric oxide (NO) was measured using an integrated LR2000 clinical real-time NO gas analyser. 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.

### Baseline data by treatment and sequence

<table>
<thead>
<tr>
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<th>Baseline by treatment</th>
<th>Baseline by sequence</th>
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<tbody>
<tr>
<td></td>
<td>BEC-HFA</td>
<td>FLU-HFA</td>
</tr>
<tr>
<td>Methacholine PD_{20} (µg)</td>
<td>97.0 (20.8)</td>
<td>96.2 (25.4)</td>
</tr>
<tr>
<td>Exhaled NO (ppb)</td>
<td>11.3 [1.9]*</td>
<td>8.3 [1.3]</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>87.9 [2.4]</td>
<td>89.1 [2.9]</td>
</tr>
<tr>
<td>OUCC (nmol/mmol)</td>
<td>7.08 [0.99]</td>
<td>6.14 [0.91]</td>
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</table>

Values are means (SE) except methacholine PD_{20}, NO, and OUCC which are expressed as geometric means (95% CI).

**Table 1** Baseline data by treatment and sequence

At the initial screening visit before the run in the mean (SE) FEV1 was 2.93 (0.19) l (93 (2)% predicted) and mean (SE) mid forced expiratory flow (FEF25–75) 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).

### 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 β2 agonist only on an as-required basis.

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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).
**Table 2** Airway and systemic data

<table>
<thead>
<tr>
<th></th>
<th>Pooled baseline</th>
<th>FLU-HFA (500 µg/day)</th>
<th>FLU-HFA (1000 µg/day)</th>
<th>BEC-HFA (500 µg/day)</th>
<th>BEC-HFA (1000 µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Airway data</strong></td>
<td></td>
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</tr>
<tr>
<td>Methacholine PD20 (µg)</td>
<td>96.6 (22.1)</td>
<td>308.3 (93.2)*</td>
<td>416.0 (145.7)*</td>
<td>231.4 (72.9)*</td>
<td>245.9 (71.0)*</td>
</tr>
<tr>
<td>Exhaled tidal NO (ppb)</td>
<td>9.7 (1.5)</td>
<td>4.8 (0.8)*</td>
<td>4.9 (0.7)*</td>
<td>4.9 (0.6)*</td>
<td>5.0 (1.1)*</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>88.5 [2.5]</td>
<td>92.8 [2.4]*</td>
<td>91.9 [2.4]*</td>
<td>92.8 [2.3]*</td>
<td>93.0 [2.2]*</td>
</tr>
<tr>
<td>Morning PEF (/l/min)</td>
<td>443 (19)</td>
<td>455 (20)*</td>
<td>457 (20)*</td>
<td>455 (21)*</td>
<td>461 (20)*</td>
</tr>
<tr>
<td><strong>Systemic data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OUCC (nmol/mmol)</td>
<td>6.59 [0.70]</td>
<td>4.78 [0.62]</td>
<td>5.62 [0.98]</td>
<td>3.91 [0.58]*</td>
<td>2.86 [0.60]*</td>
</tr>
</tbody>
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**Table 3** Airway and systemic differences between corticosteroids

<table>
<thead>
<tr>
<th></th>
<th>500 µg/day FLU-HFA v BEC-HFA</th>
<th>1000 µg/day FLU-HFA v BEC-HFA</th>
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<tbody>
<tr>
<td>Methacholine PD20</td>
<td>1.32 (0.71 to 2.45)</td>
<td>1.69 (0.94 to 3.04)</td>
</tr>
<tr>
<td>Overnight urinary cortisol/creatinine</td>
<td>1.22 (0.87 to 1.72)</td>
<td>1.97 (1.28 to 3.02)</td>
</tr>
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</table>

**Methacholine challenge**
Both doses of FLU-HFA and BEC-HFA showed significant improvements (p<0.05) in geometric mean methacholine PD20 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 FEV1, 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 PD20 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 FEV1, % predicted (93%), although this was not the case with FEF25–75 % predicted (66%). As FEF25–75 is a better index of small airway calibre than FEV1, 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 (FEV1 <60%) with BEC-HFA compared with baseline.

Although our patients had relatively normal FEV1 values, they had severe airway hyperresponsiveness in terms of their screening methacholine PD20 of 84 µg (equivalent to a PC20 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...
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 PD₁₀₀ 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 PD₁₀₀ between baseline values by sequence, this was less than the twofold difference on which the study was powered. It is difficult to separate the real effects of time and dose on methacholine PD₁₀₀, 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 PD₁₀₀ 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.19–21

One of the potential therapeutic benefits of the extra fine Beclo-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 Beclo-HFA which, like FLU-HFA, is licenced 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 Beclo-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.7 These observations are perhaps not surprising as the Beclo-HFA formulation exhibits 1.9 fold greater lung bioavailability and 2.3 fold greater cortisol suppression than the same labelled dose of the Beclo-CFC formulation.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

In summary, our study showed no difference in airway or systemic effects with Beclo-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 Beclo-HFA than with FLU-HFA, with no gain in airway efficacy. Further dose ranging studies are required with HFA formulations in more severe asthma to characterise the long term effects on end points such as exacerbations, small airway function, dynamic HPA axis measures, and bone density.

REFERENCES


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