Fluticasone propionate 100 µg bid using a non-CFC propellant, HFA 134a, in asthmatic children

Brian Lyttle MD1, John Gilles MB ChB2, Maarja Panov MD3, Andrzej Emeryk nMed4, Claire Wixon BS5 on behalf of an international study group

BACKGROUND: Secondary to phasing out chlorofluorocarbons (CFCs), the fluticasone propionate (FP) pressurized metered-dose inhaler has been formulated in a nonozone-depleting propellant, hydrofluoralkane (HFA) 134a.

OBJECTIVES: To demonstrate equivalent efficacy and safety of FP 200 µg daily propelled by HFA 134a to FP 200 µg daily propelled by CFCs 11 and 12 over a four-week treatment period in pediatric asthmatic patients.

METHODS: The study was multinational, randomized, double blind and of parallel group design. Eligible patients aged 16 years and younger were steroid naive or receiving 500 µg/day or less of beclomethasone dipropionate, budesonide or flunisolide, or 250 µg/day or less of inhaled FP. The primary efficacy variable was mean morning peak expiratory flow with equivalence determined if the 90% CIs for the treatment differences between groups were within ±15 L/min.

RESULTS: Three hundred fifteen patients (mean age 9.3±2.8 years) were randomly assigned; 158 patients received FP HFA 134a and 157 patients received FPCFC. Over the four-week treatment period, mean morning peak expiratory flow increased from baseline in both groups (14 L/min and 17 L/min, respectively), with a mean treatment difference of −2 L/min. Equivalence was demonstrated between the groups (90% CI: −6 to +3 L/min; P=0.589). Both formulations were well tolerated with no serious drug-related events.

CONCLUSIONS: FP propelled by HFA 134a has equivalent efficacy and comparable safety to FP propelled by CFC propellants at a microgram equivalent dose in pediatric asthmatic patients.

Key Words: Asthma; Fluticasone propionate; Hydrofluoralkane 134a; Pediatrics

The pressurized metered-dose inhaler (pMDI) is the most commonly prescribed asthma medication device and is a key therapeutic option for the large number of patients who suffer from asthma (1). Although pediatric patients do experience some difficulties in using the pMDI, this can be overcome by the use of a spacer device, which also reduces the potential for local side effects such as candida and hoarseness.

Chlorofluorocarbons (CFCs) 11 and 12 have been used as the propellants in pMDIs for more than 40 years (2). However, CFCs have been shown to contribute to the depletion of stratospheric ozone (3), and although the contribution of medicinal aerosols has been minimal, a search for an alternative propellant has been made. Alternative propellants have been extensively researched by the pharmaceutical industry to...
provide a replacement that has similar chemical properties and, most important, that is acceptable to patients in terms of delivery of medication, taste and smell (4). Hydrofluoroalkane (HFA) 134a (1,1,1,2-tetrafluoroethane) has been identified as one such replacement. Preclinical and clinical studies have shown it to be inert with a similar safety profile to CFC propellants (5-7).

Fluticasone propionate (FP), a topically active corticosteroid that shows little or no systemic activity after oral administration, is indicated for the prophylactic management of asthma of all severities. It is licensed as a CFC pMDI formulation for use in children with asthma, and data from clinical studies extending for up to one year have shown that it is effective and well tolerated in this population at doses of up to 200 µg/day (8,9). FP has been successfully reformulated in pMDIs with HFA 134a without the use of excipients and has been shown to have similar pharmaceutical characteristics to its CFC counterpart (6). The FP HFA 134a pMDI contains a suspension of micronized FP in the liquefied propellant HFA 134a.

This study has been conducted to evaluate the 50 µg strength HFA formulation of FP and to demonstrate that it is clinically equivalent to the 50 µg strength CFC formulation in children with asthma when administered at a daily dose of 200 µg.

PATIENTS AND METHODS

Study subjects

Patients aged four to 16 years inclusive with a documented history of reversible airways obstruction and who were either steroid naive or receiving inhaled corticosteroids (500 µg/day or less of inhaled beclomethasone dipropionate, budesonide or flunisolide, or 250 µg/day or less of inhaled FP) were eligible for the study. Patients who had required a change in their regular asthma medication, or who had required antibiotics or hospitalization for a respiratory tract infection in the four weeks before entry were excluded. Patients were required to be able to use a pMDI correctly, and to understand and complete a daily record card (DRC) and measure their peak expiratory flow (PEF) using a mini-Wright peak flow meter (Clement Clarke International Ltd, United Kingdom). Parental or guardian assistance for younger patients was permitted. At the end of the run-in period, patients were required to meet the additional criteria outlined below to demonstrate that they still had scope for improvement in their asthma control.

- Patients were required to have a forced expiratory volume in 1 s (FEV₁) or PEF value between 70% and 100% of their predicted normal value (10).
- Patients had their PEF measured in the clinic following administration of salbutamol (maximum 800 µg) via a pMDI. The mean morning PEF during the last seven days of the run-in, calculated from the DRC, had to be 90% or less of that recorded following inhalation of salbutamol. The following Polgar formulas (10) were used to calculate the predicted FEV₁:

\[
\text{Predicted FEV}_1 = 2.098 \times 10^{-6} \times \text{height}^{2.7986}
\]

\[
\text{Predicted PEF} = -425.5714 + 5.2428 \times \text{height}
\]

The percentage predicted values were calculated using the following formula:

\[
\text{Percentage predicted} = \frac{\text{observed}}{\text{predicted}} \times 100
\]

Study design

This was a multinational, multicentre, randomized, double-blind, parallel group study over a treatment period of four weeks. The study was performed in 32 centres in 12 countries. Written approval for the study was obtained from the appropriate regulatory authorities and local ethics committees for each centre. Patients attended the clinic on four occasions. Patients who satisfied the above criteria entered a 10- to 14-day run-in period, during which they continued to take their existing asthma medications.

At the end of the run-in period, eligible patients were randomly assigned to treatment by allocating the next sequential treatment number from a predefined list generated by Patient Allocation for Clinical Trials (PACT) software (GlaxoSmithKline, United Kingdom) and were given the treatment corresponding to that treatment number. Patients were randomly assigned to receive either FP 100 µg bid propelled by HFA 134a (n=158) or FP 100 µg bid propelled by CFCs (n=157), both given twice daily as 50 µg/actuation in the morning or evening. The study treatment was administered with a large volume spacer (Volumatic, Betts, United Kingdom) if required. Other inhaled corticosteroids were discontinued when the study drug was initiated. All inhaled short-acting bronchodilators were withdrawn, and salbutamol CFC pMDIs were provided for rescue relief as required. Other asthma medication could be continued throughout the study provided that the dose remained constant.

Methods

At the screening visit, after written informed consent was obtained from the child, parent or guardian, DRCs were issued to each patient to record the following information: the highest of three morning and evening PEF readings, the number of pMDI actuations (daytime and nighttime) and daytime and nighttime symptom score on a five-point scale (0 = no symptoms; 5 = symptoms so severe that patients were unable to go to school or perform normal daily activities). Spirometry was measured at clinic visits. If a patient was unable to perform an FEV₁ manoeuvre, clinic PEF was measured instead. Patients were asked to bring their PEF meter with them to the clinic for measurement of clinic visit PEF.

Safety was monitored by recording adverse events at each clinic visit. In addition, blood samples were collected at the beginning and end of the four-week treatment period, between 8:00 and 10:00, to measure serum cortisol levels, and routine biochemical and hematology parameters. Hematological and biochemical parameters were analyzed by a single central laboratory. An oropharyngeal examination took place at all clinic visits, and swabs were taken if candidiasis was suspected. Heart rate and blood pressure were measured at each clinic visit.

Analysis

The primary assessment of equivalence was based on the mean morning PEF recorded on the DRC in the intent to treat (ITT)
population, defined as all randomly assigned patients. Clinical equivalence between FP propelled by HFA 134a and FP propelled by CFCs was established if the 90% CIs for the treatment difference of mean morning PEF were within ±15 L/min (11). The primary variable was also analyzed in the per protocol population, defined as the ITT population excluding major protocol violators. The sample size was based on the mean morning PEF. Assuming a standard deviation of the treatment difference of 35 L/min, which is taken to be an average from previous studies, 120 evaluable patients per treatment group would give the study at least 90% power to demonstrate equivalence (two-sided) between the formulations using 90% CIs (12). The mean morning and evening PEFs over the four-week treatment period were analyzed using analysis of covariance, with terms for baseline, age, sex, centre and treatment. Baseline was calculated as the mean value of the last week of the run-in period. Tests for treatment interactions with previous steroid use and spacer use were performed. Clinic visit FEV₁ and PEFs were analyzed in the same manner, with baseline taken as the value recorded at the randomization visit. The Wilcoxon’s rank sum test stratified by centre using the van Elteren method (13) was used to assess treatment differences in percentage of symptom-free days (days with a symptom score below 2), and percentage of days and nights when rescue salbutamol was not required.

Serum cortisol levels measured at the beginning and end of the four-week treatment period were log transformed to satisfy normality assumptions and were analyzed using analysis of covariance as described above.

RESULTS

Patient characteristics
A total of 410 patients were enrolled, of whom 315 were randomly assigned to receive study medication. Ninety-five patients were withdrawn from the study before random assignment, mainly for failure to meet the entry criteria for random assignment because of limited scope for improvement in lung function (75 patients). The demographic characteristics of each treatment group are outlined in Table 1. The treatment groups were well matched for age, the number of patients taking inhaled steroids at the start of the study and other asthma medication throughout the study (Table 1). At random assignment, patients in both treatment groups had a similar capacity for improvement in morning PEF, expressed as a percentage of the maximum clinic visit PEF after taking salbutamol (86% in the HFA group and 85% in the CFC group). There were very few withdrawals during the treatment period – four patients in the FP HFA 134a group and two patients in the FP CFC group. The main reason for these withdrawals in both groups was noncompliance. Seventy patients were excluded from the ITT population to form the per protocol population, mainly due to receiving unpermitted medication (48 patients), with the remaining patients not meeting the entry criteria for lung function. In the per protocol population, 124 patients received FP HFA 134a and 121 patients received FP CFC.

DRC data
Baseline morning PEF was similar between the two treatment groups – 274 L/min for the FP HFA 134a group and 272 L/min for the FP CFC group. Mean morning PEF increased in both treatment groups following random assignment to FP (Figure 1). The adjusted mean increase (adjusted for baseline, centre, age and sex) from baseline at the end of four weeks was 14 L/min in the HFA 134a pMDI group and 17 L/min in the CFC pMDI group. The two formulations of FP were shown to be equivalent, with a mean treatment difference of −2 L/min and a 90% CI of −6 to 3 L/min, well within the ±15 L/min equivalence limits (Table 2). Over weeks 1 to 4, the mean morning PEF, expressed as a percentage of the maximum clinic visit PEF after treatment with salbutamol, was 91% in both groups. In both treatment groups, the improvement from baseline was seen as early as seven days after starting treatment and continued throughout the four-week treatment period (Figure 1). A similar improvement was seen in the per protocol population, with

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patient characteristics (randomly assigned population) in a study examining fluticasone propionate (FP) 100 µg bid using a nonchlorofluorocarbon (non-CFC) propellant, hydrofluoralkane (HFA) 134a, in asthmatic children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent to treat population</td>
<td>FP HFA 134a pMDI</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>158</td>
</tr>
<tr>
<td>Sex (n)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>103 (65%)</td>
</tr>
<tr>
<td>Female</td>
<td>55 (35%)</td>
</tr>
<tr>
<td>Mean age (years ± SD)</td>
<td>9.3±2.8</td>
</tr>
<tr>
<td>Patients using a spacer (n)</td>
<td>125 (79%)</td>
</tr>
<tr>
<td>Dose of inhaled corticosteroid on entry (n)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>54 (34%)</td>
</tr>
<tr>
<td>&lt;200 µg/day</td>
<td>20 (13%)</td>
</tr>
<tr>
<td>200-500 µg/day</td>
<td>83 (53%)</td>
</tr>
<tr>
<td>&gt;500 µg/day</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Patients taking FP on entry to the study (n)</td>
<td>25 (16%)</td>
</tr>
<tr>
<td>Patients taking DSCG during the study (n)</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>Patients taking inhaled long-acting beta₂-agonists during the study (n)</td>
<td>5 (3%)</td>
</tr>
</tbody>
</table>

DSCG Disodium cromoglycate; pMDI Pressurized metered-dose inhaler

Figure 1) Mean morning peak expiratory flow (PEF) (L/min) over four weeks of treatment in a study examining fluticasone propionate 100 µg bid using a nonchlorofluorocarbon (non-CFC) propellant, hydrofluoralkane (HFA) 134a, in asthmatic children. pMDI Pressurized metered-dose inhaler
Statistical analysis on the morning PEF in the ITT population for previous steroid use did not show a significant interaction. A significant interaction for spacer use, however, was observed. The results indicated that for patients not using a spacer (20% of patients in each group), more improvement was seen in patients in the FP CFC pMDI treatment group than in the FP HFA 134a pMDI group (90% CI –29 to 1 L/min; P=0.007). For patients using a spacer (80% of patients in each group), no significant interaction was observed (Table 2).

The findings for the primary variable were further supported by the results of analysis of the secondary efficacy PEF variable, which showed no difference between the two treatment groups. The treatment difference between the two groups for evening PEF was –3 L/min (90% CI –8 to 2 L/min), and for both the percentage predicted mean morning and predicted mean evening PEF, the difference was –1 L/min (90% CI –3% to 1% and 90% CI –3% to 0%, respectively) (Table 3). An increase from baseline in both days and nights when salbutamol was not required was seen over the four-week treatment period in both groups. The number of days with a symptom score less than 2 and the number of symptom-free nights also improved in both treatment groups (Table 4). There was no significant difference between the two treatment groups for any of these parameters over the four-week treatment period. A significant interaction for patients not using a spacer was also observed for the evening PEF (Table 5). For all other secondary efficacy variables, no significant interactions with spacer use were observed (Table 5).

**Clinic visit data**

At baseline, the FP HFA 134a pMDI group had an adjusted mean FEV₁ value of 1.94 L, which increased by 0.10 L at the end of four weeks. Over the same time interval, the FP CFC pMDI group also rose by 0.10 L from an adjusted baseline of 1.97 L (Table 6). The per cent predicted FEV₁ at baseline was 88% in both groups, which increased to 93% at week 4 in both groups (90% CI –3 to 1). The change from baseline in clinic PEF is shown in Table 6.
Safety

No patient was withdrawn from treatment due to an adverse event after random assignment. The most commonly reported events during treatment were upper respiratory tract infection (10 patients in each group) and headache (seven patients in the FP HFA 134a group and six patients in the FP CFC pMDI group). The incidence of pharmacologically predictable adverse events expected for inhaled corticosteroids was low and similar between the two groups. Four patients in each group reported throat irritation, three patients in the FP HFA 134a group reported hoarseness (none in the FP CFC group) and one patient had oral candidiasis in the FP CFC group (none in the FP HFA 134a group). There was no evidence to suggest any treatment effect on laboratory data or vital sign parameters for either formulation. The mean serum cortisol levels were similar at baseline and after four weeks of treatment. In the FP HFA 134a pMDI group, the baseline value was 223 nmol/L, which increased to 266 nmol/L at week 4. This compares with corresponding values of 237 nmol/L and 261 nmol/L in the FP CFC pMDI group.

**DISCUSSION**

This study demonstrated equivalent efficacy and comparable safety of FP 100 μg administered twice daily via either a HFA 134a pMDI or a CFC pMDI in pediatric patients with asthma who had demonstrable room for improvement with their existing therapy. Study design is an important factor when evaluating equivalence between the same dose of steroid at microgram equal doses. Studies should be conducted on the steep part of the dose-response curve for the primary efficacy variable evaluated and ideally should include two dose strengths (14), although this is difficult practically in pediatric asthmatic patients due to the relatively flat dose response of inhaled steroids. This study was designed to ensure that only patients with room for improvement in lung function and who were clearly on the steep part of the dose-response curve were enrolled. It was also designed in accordance with the Committee for Proprietary Medicinal Products guidelines (15) for equivalence testing between CFC and HFA products, which state that to establish efficacy, low strength HFA corticosteroid formulations should be compared with their CFC counterparts for a minimum of a four-week treatment period in a parallel group design.

National and international guidelines have given clear guidance on the use of inhaled corticosteroids in the treatment of childhood asthma (16-18). Although patients in this study had relatively mild symptoms and the majority of patients in each group were taking inhaled steroids on entry to the study, the mean morning PEF was seen to improve in both groups over the four-week treatment period. Clinical equivalence between the two groups was established for the primary vari-
able of daily morning PEF, because the preset limits of an inter-
treatment difference with 90% CIs between ±15 L/min was
achieved (11). This was supported by the data for the second-
yary efficacy variables, which demonstrated that there were no
clinically meaningful differences between the two treatment
groups. The improvement in mean morning PEF was seen after
as early as one week, which is consistent with data from previ-
ous studies with daily doses of 100 µg and 200 µg in children
with mild asthma (19-21). The magnitude of improvement was
also comparable with other published data in a study using a
daily dose of 200 µg of FP in pediatric patients with mild to
moderate asthma (21).

A statistically significant interaction between morning and
evening PEF and patients who were not using spacer devices was
observed, which suggested that patients in the FP CFC pMDI
group improved more than those in the FP HFA 134a pMDI
group. However, there were relatively few patients who were not
using spacers (approximately 20% in each group), making the
clinical relevance of this finding unclear, particularly because
recent pharmaceutical data have suggested that the dose delivery
characteristics of the FP CFC formulation is similar to the FP
HFA formulation, irrespective of spacer use (6). Furthermore,
comparable analyses of other efficacy variables, including clinical
visit PEF, did not show any evidence of such an interaction, and
no such interaction was observed in the adult study investigating
this dose of FP (22). In this short term study, the safety profile of
the FP HFA 134a formulation was found to be similar to the
CFC formulation with respect to the incidence of adverse events
and measures of hypotensive pittingural adrenal axis suppression.
The incidence of pharmacologically predictable events, such as
oral candidiasis and hoarseness, was low in both treatment
groups, possibly because most patients used a spacer, and the fre-
quency of these events was similar to other studies in this patient
population (20).

It is recognized, however, that safety is more appropriately
assessed in longer term studies, and that systemic exposure is
more reliably assessed by measures such as drug concentrations
in the blood over time, as well as overnight or 24 h urinary
cortisol, rather than morning cortisol, levels (23). However, urin-
cary cortisol measures are dependent on accurate urine volume
measurements, which would be difficult in a multicentre, out-
patient study in children. A previous study with this dose of FP
CFC formulation in children has, however, shown that there
was no effect on the mean 24 h urinary cortisol levels follow-
ning administration for one year (9).

The efficacy and safety of the FP HFA formulation has
been established in adults with all severities of asthma over
periods of up to one year (24-26). Furthermore, salbutamol
and BDP as HFA 134a formulations have also been shown to
be effective and well tolerated in children (27,28), and a
large epidemiological study has shown that there is no adverse
effect in patients changing from their salbutamol
CFC-containing pMDI to the HFA product (29). This study,
however, provides the first published data showing that the
50 µg/actuation strength of FP administered by HFA 134a is
safe and effective in children with mild asthma at a dose of
200 µg/day, and is equivalent on a dose for dose basis to the
CFC product.

REFERENCES

3. Molina MJ, Rowland FS. Stratospheric sink for
chlorofluoromethanes: chlorine atom-catalyzed destruction of
van Campen Z. Issues surrounding MDI formulation development
5. Daly RN, Byron FR, Shepherd HR, Papadopoulos E.
CFC propellant substitution: P-134a as a potential replacement
for P-12 in PMDIs. Pharm Technol 1990;14:26-33.
transition to non-CFC pressurized metered dose inhalers.
7. Denyer LH, Kirby SM, Olson P, Ventresca GR. GR106642X,
a non-chlorinated propellant for use in metered-dose inhalers:
safety, tolerability and pharmacokinetics in healthy volunteers.
Br J Clin Pharmacol 1994;37:509P-10P.
children treated with fluticasone propionate. J Pediatr
Growth during one year of treatment with fluticasone propionate
or sodium cromoglycate in children with asthma. Pediatr Pulmonol
1997;24:178-86.
12. Dillert E, Hauschue D, Steinijans VW. Sample size determination
for bioequivalence assessment by means of confidence interval.
13. van Elteren PH. On the combination of independent two sample
14. Barnes PJ, Pedersen S, Basse W. Efficacy and safety of inhaled
15. Committee for Proprietary Medicinal Products. The note for
guidance on replacement CFCs in metered dose inhalation products.
consensus report on the diagnosis and management of asthma.
17. British Thoracic Society. The British guidelines on asthma
management. 1995 review and position statement. Thorax
Crescenzi K. A placebo-controlled trial of fluticasone propionate
20. Gustafsson P, Tsimakas J, Gold M, Prinshak R, Radford M,
Fluticasone propionate and HFA 134a in children

Gillies E. Comparison of the efficacy and safety of inhaled fluticasone propionate 200 µg/day with inhaled beclomethasone dipropionate 400 µg/day in mild and moderate asthma. Arch Dis Child 1993;69:206-11.


25. Perruchoud AP, Lundback B, Yigla Y, Sykes AP. Clinical efficacy and safety of fluticasone propionate 1 mg per day administered via a HFA 134a pressurized metered dose inhaler to patients with moderate to severe asthma. Respir Med 2000;94(Suppl B):35-41.

26. Ayres JG, Miller AB, Sykes AP. Clinical efficacy and safety of fluticasone propionate 1 mg twice daily administered via a HFA 134a pressurized metered dose inhaler to patients with severe asthma. Respir Med 2000;94(Suppl B):42-50.


