Oral steroid-sparing effect of two doses of nebulized fluticasone propionate and placebo in patients with severe chronic asthma

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Inhaled steroids, delivered by metered dose aerosol and dry powder inhalers, have proved effective in reducing the need for oral steroids in patients with oral steroid-dependant asthma. This randomized, double-blind study, compared the efficacy and tolerability of nebulized fluticasone propionate (FP Nebules™), 2 mg b.d. (FP 4 mg) and 0.5 mg b.d. (FP 1 mg) with placebo, on the reduction of oral steroid requirement in 301 adult patients with oral steroid-dependent asthma.

Primary efficacy was assessed by the reduction in daily oral steroid dose. Secondary efficacy parameters included daily diary card peak expiratory flow (PEF), day and night-time symptoms and clinic lung function measurements. Safety was assessed by adverse event monitoring and serum cortisol levels.

After 12 weeks of treatment the adjusted mean ± SEM reduction in oral prednisolone was significantly greater in the FP 4 mg group (4.44 ± 0.98 mg day⁻¹) compared with FP 1 mg (2.16 ± 1.00 mg day⁻¹, P = 0.039) and placebo (1.20 ± 1.02 mg day⁻¹, P = 0.004). A higher percentage of patients discontinued the use of oral steroids with FP 4 mg (37%) compared with FP 1 mg (26%, P = 0.038) and placebo (18%, P < 0.001). Following treatment, the adjusted mean morning PEF showed a trend in favour of FP 4 mg (280 ± 4 1 min⁻¹) compared with placebo (270 ± 51 min⁻¹, P = 0.053) and the evening PEF was significantly higher with FP 4 mg (305 ± 41 min⁻¹) compared with FP 1 mg (292 ± 4 1 min⁻¹, P = 0.010). FP 4 mg resulted in a significantly higher percentage of days when the patients were free from daytime (P = 0.036) and night-time (P = 0.021) wheeze, compared with placebo. Significantly fewer patients withdrew from the FP 4 mg group compared with the other two groups (vs. FP 1 mg, P = 0.003; vs. placebo, P = 0.032). All three treatments were well tolerated and the incidence of adverse events was similar between the groups.

FP Nebules at a daily dose of between 1 and 4 mg are a safe and effective means of reducing the oral steroid requirement of patients with chronic oral steroid dependent asthma.

Introduction

The introduction of inhaled steroids two decades ago allowed many patients with severe chronic asthma to substantially reduce or discontinue the oral steroids necessary to control their disease (1). Inhaled corticosteroids such as beclomethasone dipropionate (BDP) and budesonide are well recognized as important therapies in the management of chronic asthma, but there are still patients with chronic severe asthma who cannot be adequately controlled with inhaled corticosteroids and bronchodilators and who, therefore, require maintenance treatment with oral steroids (2). Nebulized corticosteroids have been used as a means of administering high doses of corticosteroids to patients with severe asthma, including patients with acute exacerbations (3) and those with oral corticosteroid-dependant disease (4). In addition, nebulized therapy is of value in patients who have difficulty coordinating their inhalers, which is more likely to be a problem in patients with severe disease.

Fluticasone propionate (FP) is a relatively new inhaled corticosteroid (5,6), which a number of clinical trials have shown to have an improved therapeutic ratio compared with other commonly used inhaled corticosteroids (7). Such studies have demonstrated that FP is more effective at the same daily mg dose (8,9) and at least as more effective at half the dose (7,10-13) of BDP and budesonide. Crucially, FP is not appreciably absorbed from the gastrointestinal tract and undergoes high first pass metabolism, resulting in negligible oral bioavailability and hence
fewer were withdrawn for non-compliance and the remain-

ing 11 were withdrawn because they were unwilling or un-
able to return for all the necessary visits (Fig. 1).

Regulatory and ethics committee approval was obtained
for each centre before the start of the study and written
informed consent was obtained from each patient before
entry into the study. The study was conducted in
accordance with the ethical code of practice of the
declaration of Helsinki.

STUDY DESIGN

This was a multicentre, randomized, double-blind, parallel
group comparison lasting a total of 16 weeks, performed in
45 centres in 19 countries (i.e. Australia, Austria, Croatia,
Finland, Iceland, Netherlands, Norway, South Africa,
Switzerland and the United Kingdom).

There was a 2-week run-in period during which patients
remained on their existing doses of inhaled and oral
corticosteroids. Patients were allowed to repeat the run-in
once if they did not fulfil the entry criteria after the first
run-in period. Patients satisfying the entry criteria were
randomized to receive one of three nebulized treatments,
FP Nebules 2 mg twice daily, FP Nebules 0.5 mg twice daily
or placebo Nebules twice daily, for a 12-week treatment
period. During this time they continued taking their
existing inhaled corticosteroid at the same dose and their
prednisolone tablets at the reducing dose. Patients were also
issued with Ventolin™ (either a metered dose inhaler or
Diskhaler™ in accordance with their previous experience)
for use as required, for the relief of symptoms.

One of the following nebulizer bowl and compressor
combinations was supplied to each patient together with
the corresponding tubing and accessories: Sidestream and
Portaneb 50, Pari LC plus and Pari-Boy or Cirrus and
DeVilbiss: Pulmo-Aide. Each centre selected only one
nebulizer bowl and compressor combination according to
local preferences and practices. All patients were encour-
gaged to use a mouth-piece with nebulized study medication.
A face-mask could be used if the patient was unable or
unwilling to use the mouth-piece. Less than 6% of patients
used a face-mask in this study. If a face-mask was used, the
patient was asked to wash his/her face using a barrier cream.

Treatment randomizations were achieved using a
computerized scheme written in Fortran called 'Patient Alloca-
tion for Clinical Trials' (PACT). A follow-up visit was
conducted 2 weeks following the completion of the
treatment period to ensure patient safety.

METHODS

Primary efficacy was measured by the reduction in oral
prednisolone doses achieved by the patients while asthma
stability was maintained. Investigators were asked to
document whether the patient had attempted to reduce
their oral corticosteroid dose in the previous 6 months to
confirm the patient's need for the current dose. At each
fortnightly visit during the treatment period, the investi-
gator assessed the stability of the patient's asthma and
reduced the daily doses of oral prednisolone by 2.5 mg (or

Patients and methods

PATIENTS

A total of 360 male and female patients, aged 17 years or
over, with an established history of severe chronic asthma
requiring treatment with oral corticosteroids and β2 agonist
therapy were enrolled into the study. Patients were required
to be on continuous oral corticosteroid therapy for at least
3 months before entry to the study. All were outpatients,
who in addition to receiving oral corticosteroids at a dose of
at least 5 mg day⁻¹ (or 10 mg every second day), but no
more than 30 mg day⁻¹ (or 60 mg every second day), could
be receiving either no inhaled corticosteroid or up to and
including 2 mg day⁻¹ inhaled beclomethasone dipropionate
or budesonide or up to and including 1 mg day⁻¹ inhaled
FP. In the 2 week run-in phase of the study, patients were
required to demonstrate either a diurnal variation of at
least 15% in PEF, or at least 4 days of the run-in period, or
reversibility in forced expiratory volume in 1s (FEV₁) with
salbutamol of at least 15%. Patients were excluded if they
had changes in their regular asthma medication (i.e. inhaled
corticosteroids, oral corticosteroid or other inhaled or oral
therapies), had an upper or lower respiratory tract infection
requiring treatment with antibiotics, a hospital admission
for respiratory disease in the 4 weeks before the run-in
period, an exacerbation of asthma during the run-in period
which required additional oral corticosteroid treatment, a
history or laboratory data indicative of serious clinical
systemic disease, a serious psychological disorder or any
disease likely to interfere with the objectives of this study.
Patients were also excluded if they had any known or
suspected hypersensitivity to corticosteroids or if they had
received any other investigational drug within the previous
4 weeks. Three hundred and one patients were randomized
to receive treatment; 103 received FP Nebules 2 mg b.d. (FP
4 mg), 102 received FP Nebules 0.5 mg b.d. (FP 1 mg) and
96 received placebo Nebules b.d. Fifty nine patients were
withdrawn before randomization, of which 26 failed to
meet the entry criteria at the end of the run-in period, 18
experienced an adverse event during the run-in period,
fewer were withdrawn for non-compliance and the remain-

Reduced potential for systemic effects (5). Its use should
allow patients with more severe asthma to reduce or
discontinue their need for oral corticosteroids (14), thus
minimizing the risk of systemic corticosteroid side effects
(15).

Fluticasone propionate has now been formulated in
Nebules™ for administration by nebulization. Nebulizers
provide a convenient means of delivering high doses of
corticosteroids at low inspiratory flow rates (i.e. using tidal
breathing) without the need for patients to co-ordinate any
essential manoeuvres or to hold their breath (16). This
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5 mg on alternate days) each time if the patient's asthma was stable relative to his/her normal level of symptoms and lung function (i.e. their symptom score, day or night had not increased by more than one on three consecutive days, either within the preceding 14 days, or compared with the daily record (diary) card returned at the previous visit and neither their morning PEF nor their evening PEF had fallen by more than 10%). In addition, the investigator needed to be satisfied that a dose reduction was acceptable to the patient. If a faster dose reduction was appropriate for the
patient, then the daily dose of oral prednisolone could be reduced by 5 mg (10 mg if taken on alternate days) each time for patients who were taking a daily prednisolone dose of greater than 10 mg day$^{-1}$ (20 mg on alternative days), after which the dose reduction was by 2.5 mg (5 mg if taken on alternate days) once the daily dose had been reduced to 10 mg day$^{-1}$ (20 mg on alternate days) or below.

Additional efficacy assessments were based on daily measurement of PEF and daily recording of daytime and night-time asthma symptom scores recorded in a diary card by the patients and on pulmonary function tests performed at each clinic visit.

**IN VITRO NEBULIZER STUDIES**

*In vitro* testing using a cascade impactor, prior to starting the study, demonstrated that the respirable fractions (i.e. particle sizes of between 2 μ to 6 μ, as % of mean content) from 2 ml of the 2 mg 2 ml$^{-1}$ Nebules used according to their respective manufacturer's instructions for the Side-stream/Portaneb 50, Pari LC plus/Pari-Boy and Cirrus/Devilbiss: Pulmo-Aide nebulisers were 14.9%, 11.9% and 16.2%, respectively.

**ADVERSE EVENTS**

All adverse events were recorded, whether serious or minor and irrespective of their causality. Serious adverse events were defined as: death, life threatening events, disabling or incapacitating events, events which required or prolonged hospitalization, a resulting congenital abnormality, cancer, drug overdose, and any serious laboratory abnormality that was associated with clinical signs or symptoms.

**LABORATORY EVALUATIONS**

Venous blood samples were collected during the clinic visits at baseline and after 6 and 12 weeks of treatment for the evaluation of haematology and biochemical parameters and serum cortisol. Where possible, samples were taken between 08:00 and 10:00 h. Separate analyses for serum cortisol were performed for all samples and for samples collected between 08:00 and 10:00 h, as required by the protocol. The result obtained for each test parameter was also compared to a predefined set of laboratory threshold values. The threshold values lie outside the normal range (i.e. lower threshold $<$0.67×lower limit of the normal range) and are regarded as potentially important reductions or increases in the test parameter. All samples were analysed centrally (CORNING Hazleton, Harrogate, U.K.) using the TDX Cortisol™ fluorescence polarisation immunoassay (Abbott Laboratories, Abbott Park, Illinois, U.S.A.)

**ANALYSIS**

Statistical analyses were carried out using SAS version 6.08 (SAS Software Limited, Marlow, U.K.). Hypothesis tests looked at all of the pair-wise comparisons between the three treatment groups. Treatment differences were assessed using two-sided significance tests, based at the 5% significance level. For the purpose of analysis, the centres were amalgamated into nine clusters according to geographical regions, in order to provide adequate patient numbers within each group. Based on a standard deviation of 8.5 mg day$^{-1}$, and a clinical difference between treatments of 5 mg day$^{-1}$ in reduction of oral steroid usage, then a total of 100 patients per treatment would ensure that the study had 80% power in detecting such a difference at the 5% significance level.

The analysis of oral corticosteroid reduction (absolute change from start of treatment) was carried out using patients’ last available data recorded whilst taking study treatment and using analysis of covariance with the dose at randomization and age taken as covariates. Variations due to country, sex and model of nebulizer were also accounted for in the model. Significant two-factor interactions with treatment were explored. The assumption of normality was not satisfied when analysing oral steroid percentage reduction from start of treatment, therefore the Van-Elteren extension to the Wilcoxon rank sum test was used, with country as a stratifying variable in the analysis. The confidence limits were calculated using an unstratified Wilcoxon rank sum test. A weighted mean oral corticosteroid consumption (based on area under the curve) was calculated for each patient over the 12 week treatment period. Patients not recording a measurement at the end of the 12 week treatment period had their last available measurement carried forward. The derived weighted mean was analysed using analysis of covariance for absolute change in oral corticosteroid usage.

Mean morning PEF, mean evening PEF and mean percentage diurnal variation in PEF were derived, with the denominator based on the number of days where morning/evening PEF was recorded. Derived PEF values were then investigated using analysis of covariance, with the respective mean lung function, taken over the final week of run-in, and age taken as covariates. Variations due to country, sex and model of nebulizer were also accounted for in the model. Significant two-factor interactions with treatment were explored. The Van Elteren extension to the Wilcoxon rank sum test was used to assess pair-wise differences between the treatment groups for each symptom variable and the use of rescue medication. Serum cortisol values were log-transformed prior to analysis and the difference between treatments was expressed as a ratio between treatments. The latter were analysed using analysis of covariance.

**Results**

Patient characteristics at baseline are shown in Table 1. One hundred and three patients received FP 2 mg b.d. (FP 4 mg), 102 received FP0.5 mg b.d. (FP 1 mg) and 96 received placebo. The three treatment groups were well-matched with respect to demographic characteristics, history of asthma, concurrent medication and daily dose of oral
Table 1. Patient characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FP 4 mg day⁻¹ (2 mg b.d.)</th>
<th>FP 1 mg day⁻¹ (0.5 mg b.d.)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients n</td>
<td>103</td>
<td>102</td>
<td>96</td>
</tr>
<tr>
<td>Sex n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>51(50)</td>
<td>58(57)</td>
<td>55(57)</td>
</tr>
<tr>
<td>Females</td>
<td>52(50)</td>
<td>44(43)</td>
<td>41(43)</td>
</tr>
<tr>
<td>Age n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16&lt;40</td>
<td>17(17)</td>
<td>14(14)</td>
<td>12(13)</td>
</tr>
<tr>
<td>40&lt;65</td>
<td>58(56)</td>
<td>54(53)</td>
<td>59(61)</td>
</tr>
<tr>
<td>≥65</td>
<td>28(27)</td>
<td>34(33)</td>
<td>25(26)</td>
</tr>
<tr>
<td>Age range (yrs)</td>
<td>19-83</td>
<td></td>
<td>20-76</td>
</tr>
<tr>
<td>Duration of asthma n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5 yrs</td>
<td>9(9)</td>
<td>24(24)</td>
<td>14(15)</td>
</tr>
<tr>
<td>6-10 yrs</td>
<td>25(24)</td>
<td>77(76)</td>
<td>71(72)</td>
</tr>
<tr>
<td>&gt;10 yrs</td>
<td>69(67)</td>
<td>51(50)</td>
<td>61(64)</td>
</tr>
<tr>
<td>Tobacco use n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>47(46)</td>
<td>43(42)</td>
<td>33(34)</td>
</tr>
<tr>
<td>Former user</td>
<td>45(44)</td>
<td>47(46)</td>
<td>52(54)</td>
</tr>
<tr>
<td>Current user</td>
<td>11(11)</td>
<td>12(12)</td>
<td>11(11)</td>
</tr>
<tr>
<td>Concurrent medications n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroid</td>
<td>89(86)</td>
<td>85(83)</td>
<td>83(86)</td>
</tr>
<tr>
<td>Inhaled long-acting β₂-agonist</td>
<td>55(23)</td>
<td>47(20)</td>
<td>50(21)</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>51(22)</td>
<td>49(21)</td>
<td>51(21)</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>26(11)</td>
<td>36(15)</td>
<td>42(18)</td>
</tr>
<tr>
<td>Cromoglicate</td>
<td>8(3)</td>
<td>7(3)</td>
<td>7(3)</td>
</tr>
<tr>
<td>Ketotifen</td>
<td>0(0)</td>
<td>1(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Other asthma medication</td>
<td>6(3)</td>
<td>5(2)</td>
<td>5(2)</td>
</tr>
<tr>
<td>Oral steroid usage n (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 mg daily</td>
<td>1(&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5-&lt;10 mg daily</td>
<td>46(45)</td>
<td>51(50)</td>
<td>38(40)</td>
</tr>
<tr>
<td>10-&lt;20 mg daily</td>
<td>45(44)</td>
<td>8(37)</td>
<td>49(51)</td>
</tr>
<tr>
<td>20-30 mg daily</td>
<td>11(11)</td>
<td>8(13)</td>
<td>9(9)</td>
</tr>
</tbody>
</table>

FP: fluticasone propionate.

*approximately 10% of patients took their oral steroid dose on alternate days but the equivalent daily dose is included in the table.

steroid at entry to the study; Between 83% and 86% of patients in each treatment group were taking inhaled corticosteroids (i.e. FP, beclomethasone dipropionate, budesonide, flunisolide) during the 12 weeks of the study. The mean ±SD daily doses of inhaled corticosteroids in the three treatment groups were similar (i.e. 1409±554 mg day⁻¹(FP 4 mg), 1460±635 mg day⁻¹(FP 1 mg), 1389±649 mg day⁻¹(placebo)).

ORAL PREDNISOLONE REDUCTION

The results of oral steroid usage are shown in Table 2. At randomization, patients in the FP 4 mg group received a mean±SEM daily oral prednisolone dose of 10.3±5.8 mg day⁻¹, which decreased to 5.3±7.5 mg day⁻¹ after 12 weeks of treatment, a mean reduction of 5.0±7.5 mg day⁻¹. Over the same period, patients in the FP 1 mg group decreased their mean daily dose from 9.5±5.6 mg day⁻¹ to 6.2±8.1 mg day⁻¹, a mean reduction of 3.9±8.3 mg day⁻¹, and the placebo group dose decreased from 10.3±5.9 mg day⁻¹ to 7.4±7.8 mg day⁻¹, a mean reduction of 2.6±8.6 mg day⁻¹.

The adjusted mean±SEM reductions in oral corticosteroid dose from baseline to the last available dose recorded whilst receiving study treatment were 4.4±1.0 mg day⁻¹, 2.2±1.0 mg day⁻¹ and 1.2±1.0 mg day⁻¹ for the FP 4 mg, FP 1 mg and placebo groups, respectively (Fig. 2). There was a significantly greater reduction in the FP 4 mg group compared with the placebo group (P=0.004) and the FP 1 mg group (P=0.039). No significant difference was found between FP 1 mg and placebo (P=0.400).

The median percent reduction in daily oral steroid dose was 66-7% with FP 4 mg, 50-0% with FP 1 mg and 22-5% with placebo. There was a significantly greater reduction in
TABLE 2. Effect of treatment on mean daily oral steroid dose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FP 4 mg day⁻¹</th>
<th>P-value vs. placebo</th>
<th>FP 1 mg day⁻¹</th>
<th>P-value vs. placebo</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD prednisolone dose (mg day⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.3±5.8</td>
<td>9.5±5.6</td>
<td>10.4±5.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>5.3±7.6</td>
<td>6.2±8.1</td>
<td>7.4±7.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in oral steroid use (mg day⁻¹)</td>
<td>5.0±7.5</td>
<td>3.9±8.3</td>
<td>2.0±8.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted mean ± SEM reduction (mg day⁻¹)</td>
<td>4.4±0.98</td>
<td>2.2±1.0</td>
<td>0.400</td>
<td>1.2±1.0</td>
<td></td>
</tr>
<tr>
<td>Median reduction (%)</td>
<td>66.7</td>
<td>&lt;0.001</td>
<td>50.0</td>
<td>0.259</td>
<td>22.5</td>
</tr>
</tbody>
</table>

FP: fluticasone propionate; SD: standard deviation; SEM: standard error of the mean.

The FP 4 mg group compared with the placebo group (P<0.001) and compared with the FP 1 mg group (P=0.038). No significant difference was found between FP 1 mg and placebo (P=0.259). The number of patients who completed the study and entirely discontinued the use of oral steroids was 37 (37%) in the FP 4 mg group, 25 (26%) in the FP 1 mg group (P=0.038 for FP 4 mg vs. FP 1 mg) and 16 (18%) in the placebo group (P<0.001 for FP 4 mg vs. placebo) (Fig. 3).

DAILY PEF

The mean ± SD increases in morning PEF following 12 weeks of treatment in the FP 4 mg, FP 1 mg and placebo groups were 27±52 min⁻¹, 12±53 min⁻¹ and 12±42 min⁻¹ respectively (Table 3). There was a trend for greater improvement in favour of FP 4 mg versus placebo for morning PEF (P=0.053). The mean increases in evening PEF following 12 weeks of treatment in the FP 4 mg, FP 1 mg and placebo groups were 21±56 1 min⁻¹, 6±45 1 min⁻¹ and 10±39 1 min⁻¹, respectively. Evening PEF following treatment was significantly higher in the FP 4 mg group compared with the FP 1 mg group (P=0.010). There was a trend for greater improvement in favour of FP 4 mg versus placebo (P=0.060).

CLINIC LUNG FUNCTION

Clinic PEF and FEV₁ increased in all three treatment groups during the study, but there was no significant differences between the treatments (Table 3). The mean increases in morning PEF following 12 weeks of treatment in the FP 4 mg, FP 1 mg and placebo groups were 24±78 1 min⁻¹, 7±63 1 min⁻¹ and 22±57 1 min⁻¹ respectively. The mean increases in FEV₁ following 12 weeks of treatment in the FP 4 mg, FP 1 mg and placebo groups were 0.14±0.47 l, 0.07±0.34 1 and 0.06±0.38 1 respectively.

SYMPTOM SCORES

The results of the symptom scores are tabulated in Table 4. FP 4 mg resulted in a significantly higher percentage of days when the patients were free from daytime (P=0.036) and night-time (P=0.021) wheeze compared with the placebo group, and a trend for a higher percentage of symptom-free nights (P=0.075) compared with the FP 1 mg group. The percentage of days when patients were free from daytime shortness of breath was significantly higher in the FP 4 mg group compared with the placebo (P=0.036). The percentage of nights when patients were not awoken due to asthma was significantly higher in the FP 4 mg compared with the placebo group (P=0.008) with a trend compared with the FP 1 mg (P=0.033) group.

Similar numbers of patients used the Sidestream (36–37%), Pari LC plus (54–57%) and Cirrhus (69%) nebulizers in the three treatment groups (Table 5). In addition, similar numbers of patients used a mouth-piece (94–97%) and face-mask (3–6%).

Statistical analyses were performed allowing for variations due to the type of nebulizer in the model. No significant treatment interactions were seen between the efficacy and safety variables and use of different nebulizers.
Safety

ADVERSE EVENTS

The overall incidence of adverse events was similar in all three treatment groups (79% of patients receiving FP 4 mg, 76% of patients receiving FP 1 mg and 77% of patients receiving placebo). The most commonly reported adverse events were either respiratory in nature or predictable adverse events. The incidence of these adverse events differed between the groups (Table 4). More patients in the placebo (10%) and FP 1 mg (10%) groups had asthma exacerbations which were serious or resulted in the patients being withdrawn from the study than in the FP 4 mg (2%) group. There were more predictable adverse events in the FP 4 mg group than in the other two groups, although oral candidiasis was reported by more patients in the FP 1 mg group (14%) than the FP 4 mg group (12%) or placebo group (8%). A total of 32 patients withdrew from the study due to an adverse event; most of the withdrawals were due to an exacerbation of asthma. Fewer patients withdrew from the FP 4 mg group in which 5 (5%) withdrew due to an adverse event, compared with 15 (15%) patients in the FP 1 mg and 12 (13%) in the placebo group. The difference between the numbers of patients who withdrew from the study were significant between FP 4 mg and FP 1 mg (P=0.003) and FP 4 mg and placebo (P=0.032).

Serious adverse events during treatment were reported by a total of 28 patients (28%), six in the FP 4 mg group, nine in the FP 1 mg group and 13 in the placebo group. In each treatment group, the majority of events were related to respiratory conditions. Serious adverse events were considered by the investigator to be drug related in only two patients, the first patient had been randomized to the placebo group and the second patient to the FP 1 mg group. Both patients had an asthma exacerbation which was assessed by the investigator as 'possibly related' to the study medication. One patient withdrew from the FP 4 mg group due to a serious adverse event compared with seven from the FP 1 mg group and six from the placebo group.

Two patients died during the study. One patient, who had been receiving FP 4 mg, died during the post-treatment period after developing gastric bleeding, considered by the investigator to be unrelated to study medication and the other patient, in the placebo group, developed status asthmaticus.

LABORATORY RESULTS

When all the samples were compared, the geometric mean (coefficient of variation (CV) %) concentrations at baseline were 192 (66%) nmol l⁻¹ in the FP 4 mg group, 208 (48%) mol l⁻¹ in the FP 1 mg group and 181 (56%) nmol l⁻¹ in the placebo group. After 6 weeks of treatment, the mean values had decreased in all the groups, but after 12 weeks of treatment the mean values had decreased to 164 (72%) mol l⁻¹ in the FP 4 mg group, decreased to 205 (49%) nmol l⁻¹ in the FP 1 mg group and increased to

TABLE 3. Mean ± SD lung function results before (BL) and after (Post-Rx) 12 weeks of treatment

<table>
<thead>
<tr>
<th>Lung function parameter</th>
<th>FP 4 mg</th>
<th>P-value</th>
<th>FP 1 mg</th>
<th>P-value</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diary card PEF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>am PEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(l min⁻¹)</td>
<td>252 ± 101</td>
<td>281 ± 108</td>
<td>P = 0.053</td>
<td>273 ± 94</td>
<td>291 ± 101</td>
<td>P = 0.765</td>
</tr>
<tr>
<td>pm PEF</td>
<td>276 ± 102</td>
<td>299 ± 104</td>
<td>P = 0.060</td>
<td>302 ± 101</td>
<td>310 ± 104</td>
<td>P = 0.497</td>
</tr>
<tr>
<td><strong>Clinic lung function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>am PEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(l min⁻¹)</td>
<td>272 ± 107</td>
<td>297 ± 112</td>
<td>P = 0.350</td>
<td>293 ± 105</td>
<td>307 ± 114</td>
<td>P = 0.821</td>
</tr>
<tr>
<td>FEV₁(L)</td>
<td>1.57 ± 0.70</td>
<td>1.71 ± 0.71</td>
<td>P = 0.261</td>
<td>1.63 ± 0.75</td>
<td>1.71 ± 0.80</td>
<td>P = 0.711</td>
</tr>
</tbody>
</table>

* Significantly different from FP 1 mg (P=0.038).
† Significantly different from placebo (P<0.001).
TABLE 4. Symptom scores (median percentage symptom free days/nights) following treatment

<table>
<thead>
<tr>
<th>Symptom</th>
<th>FP 4 mg</th>
<th>FP 4 mg vs. placebo P-value</th>
<th>FP 1 mg</th>
<th>FP 1 mg vs. placebo P-value</th>
<th>Placebo</th>
<th>FP 4 mg vs. FP 1 mg P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td></td>
<td>0.536</td>
<td>0.542</td>
<td></td>
<td>0.994</td>
<td></td>
</tr>
<tr>
<td>Chest tightness</td>
<td></td>
<td>0.559</td>
<td>0.516</td>
<td></td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Wheeze</td>
<td></td>
<td>0.225</td>
<td>0.869</td>
<td></td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td></td>
<td>0.021</td>
<td>0.551</td>
<td></td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Nights not awoken by symptoms (%)</td>
<td>0.008</td>
<td>0.752</td>
<td>0.64</td>
<td></td>
<td>0.053</td>
<td></td>
</tr>
</tbody>
</table>

FP: fluticasone propionate
D: day
N: night

TABLE 5. Nebulizer use in three treatment groups

<table>
<thead>
<tr>
<th>Nebulizer</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>96</td>
</tr>
<tr>
<td>FP 1 mg</td>
<td>102</td>
</tr>
<tr>
<td>FP 4 mg</td>
<td>103</td>
</tr>
<tr>
<td>Pari LC plus/Pari Boy</td>
<td>55(57%)</td>
</tr>
<tr>
<td>Sidestream/Portaneb</td>
<td>35(36%)</td>
</tr>
<tr>
<td>Cirrus/DeVilbiss</td>
<td>6(6%)</td>
</tr>
<tr>
<td>Face-mask</td>
<td>3(3%)</td>
</tr>
<tr>
<td>Mouth-piece</td>
<td>93(94%)</td>
</tr>
</tbody>
</table>

200 (47%) nmol 1⁻¹ in the placebo group. After 6 weeks of treatment, there were no significant differences between the treatments. Following 12 weeks of treatment, the adjusted mean serum cortisol value was significantly lower in the FP 4 mg group compared with the placebo group (P = 0.036). A similar pattern of serum cortisol changes was seen for samples collected between 08:00 to 10:00 h. The geometric mean cortisol values in the patients who stopped taking oral steroids at the beginning and end of treatment, respectively, were: 216 (59.1%) nmol 1⁻¹ and 221 (55.4%) nmol 1⁻¹ in the FP 4 mg group, 238 (39.7%) nmol 1⁻¹ and 283 (29.3%) nmol 1⁻¹ in the FP 1 mg group and 179 (52.7%) nmol 1⁻¹ and 207 (46.4%) nmol 1⁻¹ in the placebo group. There were no significant differences between the three treatment groups. Only eight (8.0%) patients in FP 4 mg group had serum cortisol values that were below the threshold value at the end of treatment, compared with six (7.0%) in the placebo group. No clinical effects related to changes in serum cortisol values were seen in any of the patients.

Discussion

The primary aim of this study was to compare the efficacy and safety of nebulized FP 4 mg day⁻¹ and 1 mg day⁻¹ with placebo in the reduction of oral steroids required in adult patients with chronic oral steroid dependent asthma, while maintaining asthma stability. Patients, whose asthma was in a stable phase such that they had not had an asthma exacerbation during the previous month, gradually tried to substitute the oral portion of their corticosteroid therapy with nebulized treatment. Patients must have required continuous oral steroid therapy for 3 months before entering the study and for 6 of the previous 12 months in order to be eligible, thereby establishing their dependence on oral steroids. At the end of the 12 weeks of treatment there was a significant dose-related reduction in oral steroid requirements, with a rank order of FP 4 mg > FP 1 mg > placebo. Significantly more patients receiving FP 4 mg were also able to discontinue their need for oral steroid
completely compared with the other two groups, confirming the value of nebulized FP as an effective replacement therapy for oral steroid. This result supports the findings of Noonan et al. (14), who demonstrated a significant dose-related reduction in oral steroid requirements in patients with oral steroid dependent asthma treated with FP 1.5 mg day$^{-1}$ and 2.0 mg day$^{-1}$ by a metered dose inhaler.

Clinic lung function measured by PEF and FEV$_1$ improved in all three groups over the 12 week treatment period, but was best in the FP 4 mg group, although the differences between the groups were not significant. The diary card PEF results showed a greater separation of the doses, such that after 12 weeks of treatment, the difference in improvement between the FP 4 mg and placebo groups was statistically significant for evening PEF and approached significance for morning PEF. The study was designed to maintain control of the patients' asthma whilst they reduced their daily dose of oral steroid. In fact, if anything, the patients' lung function tended to improve, in a dose-related manner, suggesting improved disease control, despite a significant reduction in oral steroid requirements. In addition, there were more withdrawals in the placebo group due to exacerbations compared with the FP 4 mg group, leaving fewer more severely affected patients in the placebo group at the end of the study. These withdrawals from the placebo group may have biased the results on lung function, as well as on the other efficacy parameters, against the active treatment.

In addition to the improvements in lung function seen during FP treatment, patients showed significant improvements in their symptom scores recorded in diary cards. Patients receiving FP 4 mg had significantly fewer days and nights with wheeze, significantly fewer days with shortness of breath and significantly more nights when they were not woken by their asthma, than patients receiving placebo. These improvements in symptoms support those seen in objective measures of lung function and support a clinically meaningful benefit of nebulized FP in these patients.

By contrast with the results from this double-blind, placebo-controlled study in a large number of patients, the oral steroid sparing effect of nebulized budesonide has been studied in two small, uncontrolled studies. In the first study, 42 adults with chronic oral steroid dependent asthma received 12 weeks of treatment with nebulized budesonide 2 mg day$^{-1}$ in an open study (17). At the end of this period, 23 patients (55%) were able to reduce their oral steroid requirement significantly (mean reduction of 59% from initial dose of 12.5 mg) while maintaining their lung function. None was able to discontinue their oral steroids completely. In the second open study, which used higher doses of nebulized budesonide (between 4 and 8 mg daily) over a longer treatment period (up to 18 months), 14 (78%) patients successfully stopped oral steroids, while maintaining their lung function (4). These data support the findings of the present large, placebo-controlled study with nebulized FP and suggest a role for nebulized steroids in the treatment of oral steroid dependent patients with asthma.

Three different nebulizers (i.e. Sidestream/Portaneb 50, Pari LC plus/Pari-Boy and Cirrus/DeVilbiss: Pulmo-Aide) commonly used in Europe, were utilized in the study. All were found to work effectively with FP Nebules producing respirable aerosols, with good output of drug and similar mass median aerodynamic diameters. The use of different nebulizers did not significantly influence the effect of treatment on primary efficacy or cortisol values, confirming the clinical effectiveness of all three nebulizers with FP Nebules in this patient population.

After randomization, 52 patients were withdrawn from the study. Most of these patients were withdrawn due to an adverse event, generally related to a lower respiratory tract condition. Significantly fewer patients were withdrawn from the FP 4 mg group than from either of the other two groups, indicating better overall disease control and in line with the greater improvements in lung function and symptoms in this group.

Nebulized FP 1 mg and 4 mg daily were as well tolerated as placebo throughout the study. The overall incidence of adverse events was similar in all the treatment groups, and those which were reported most commonly were of a respiratory nature or were predictable adverse events. The most common predictable adverse event was candidiasis of the mouth or throat. This was reported by 12% of patients in the FP 4 mg group, 14% in the FP 1 mg group and 8% in the placebo group, and these frequencies of candidiasis are anticipated in oral corticosteroid dependent patients on high doses of inhaled steroids (18). Serious adverse events during treatment were reported by 28 patients, 13 (14%) in the placebo group, nine (9%) in the FP 1 mg group and six (6%) in the FP 4 mg group. In the majority of these patients a respiratory adverse event was reported, suggesting a dose-related trend for improvement in control of the patients' asthma by nebulized FP.

The mean serum cortisol values for the patients in all three treatment groups were at the lower end of the normal range at the start of treatment, consistent with the use of regular oral steroids, in many cases, for a number of years. After 12 weeks of treatment the mean cortisol value in the FP 4 mg group was lower than in the placebo and FP 1 mg groups, but remained within the normal range, despite being at the lower end of the normal range at the start of treatment. There were no clinical signs or symptoms or laboratory abnormalities associated with this fall in serum cortisol and its clinical importance is doubtful. In addition, in the patients who were able to stop taking oral steroids on account of treatment with nebulized FP (4 mg and 1 mg), serum cortisol levels did not fall but tended to increase. The continuing need for higher doses of oral steroids as opposed to inhaled steroids, seen in the placebo group, would be likely to result in other clinically important systemic side effects, such as reduction in bone density and thinning of the skin, were this to continue long term (19). Relevant to this, a recent prospective, double-blind, placebo-controlled, multicentre study, demonstrated that FP 1 mg day$^{-1}$ via an MDI had no effect on bone density over a 2 year treatment period (20).

One potential complicating factor in the interpretation of the serum cortisol values between the three groups is the recognised cross-reactivity of prednisolone (up to 24%) in the immunoassay used to measure cortisol in this study.
(TDx Cortisol™ fluorescence polarisation immunoassay: Abbott Laboratories, Abbott Park, Illinois, U.S.A.). It is possible that the higher dose of oral prednisolone required by the placebo group may have spuriously raised the measured cortisol value in this group and thereby accentuated any apparent difference between the placebo and FP treatment groups.

In conclusion, this large, placebo-controlled study comparing nebulized FP 2 mg b.d. FP 0.5 mg b.d. and placebo-over 12 weeks of treatment, demonstrated that the use of FP Nebules™ was associated with a significant reduction in oral prednisolone requirement in patients with oral corticosteroid dependent asthma. After 12 weeks of treatment there was a dose-related reduction in oral corticosteroid use, with 37% of patients in the FP 2 mg b.d. group being able to stop their oral steroids completely. FP Nebules™ at a daily dose between 1 mg and 4 mg are a safe and effective means of reducing the oral corticosteroid requirement of dependent patients with severe chronic asthma.

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