Comparable effects of inhaled fluticasone propionate and budesonide on the HPA-axis in adult asthmatic patients

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This randomized, double-blind, double-dummy, multicentre cross-over study compared the effects on the hypothalamic-pituitary-adrenal (HPA) axis of fluticasone propionate (750 μg twice daily given via the Diskus™ and budesonide (800 μg twice daily given via the Turbuhaler™. Two treatment periods of 2 weeks each were preceded by a 2-week run-in period and separated by a 2-week washout period. During run-in and washout, patients received beclomethasone dipropionate (BDP) or budesonide at a constant dose of 1500–1600 μg day⁻¹. Sixty patients aged 18–75 years with moderate to severe asthma not fully controlled by treatment with 1500–1600 μg day⁻¹ budesonide or BDP entered run-in and 45 completed the study. HPA axis suppression was assessed by morning serum cortisol (area under the curve from 08:00 to 10:30 hours) and 12-h nocturnal urinary cortisol excretion, measured at the end of run-in (baseline 1), at the end of washout (baseline 2), and at the end of each treatment period.

Neither budesonide nor fluticasone produced significant suppression of either parameter compared to baselines. Only a few patients had serum-cortisol and urinary cortisol values below the normal range, before and after treatment. This shows that the patients did not have adrenal suppression before entering the study. The ratio between the AUC serum cortisol measured after fluticasone treatment and after budesonide treatment was 0.99 (95% CI 0.92–1.06), indicating equivalent effects on the HPA axis. This result was achieved after having omitted two patients’ results, due to their very sensitive reaction to budesonide, but not to fluticasone. Two exacerbations of acute asthma occurred during budesonide treatment and none during fluticasone treatment. Both treatments were well tolerated. In conclusion, budesonide 1600 μg day⁻¹ via Turbuhaler™ and fluticasone propionate 1500 μg day⁻¹ via Diskus™ had no clinical effects on the HPA axis in patients with moderate to severe asthma.

Key words: fluticasone propionate; budesonide; HPA axis.

Introduction

Inhaled corticosteroids are now well established in the treatment of asthma, and are considered to have an essential role in the management of most asthmatic patients (1). Guidelines on asthma management published in Europe and the U.S.A. recommend the use of inhaled corticosteroids as first-line therapy in all but the mildest cases of asthma (2,3).

Although inhaled corticosteroids have a far lower potential for systemic effects than oral corticosteroid therapy, this potential is not zero and the systemic effects of long-term inhaled corticosteroid therapy have been much studied in recent years (for a review, see reference 1). Long-term therapy at high doses may sometimes produce
clinically evident systemic effects, such as skin thinning or easy bruising (4,5). Other potential systemic effects include suppression of the hypothalamic-pituitary-adrenal (HPA) axis, reduced bone density and growth impairment in children (6). Of these, HPA suppression is the most sensitive and easily measured marker of the systemic activity of inhaled corticosteroids (1).

Systemic exposure to inhaled corticosteroids occurs via two routes. Part of an inhaled dose is deposited in the lower airways and absorbed into the pulmonary circulation. The remainder, which may be up to 80% (7), is deposited in the mouth and on the back of the throat. Unless rinsed out, it will eventually be swallowed and absorbed through the gut. Some may be inactivated by first-pass metabolism in the liver, and the rest will reach the systemic circulation.

At the doses required by most adult asthmatics, up to approximately 800 \( \mu g \) day\(^{-1} \) of beclomethasone dipropionate (BDP) or budesonide (BUB), inhaled corticosteroids have an excellent safety profile (8). However, in adults with moderate to severe asthma, doses of up to 2000 \( \mu g \) day\(^{-1} \) of BDP may be required to achieve satisfactory disease control (3). Significant HPA axis suppression has been observed in adults receiving BDP at doses in excess of 1000 \( \mu g \) day\(^{-1} \) (9) or 1500 \( \mu g \) day\(^{-1} \) (6). Therefore, there is a need for an inhaled corticosteroid with high potency but low potential for systemic effects, even at high doses.

Fluticasone propionate (FP) has the highest receptor affinity of the inhaled corticosteroids in clinical use (10–12) and has been shown to be more potent than either BDP or BUD in a variety of in vitro models (13–17). These results are supported by clinical studies, which consistently report that FP is at least as efficacious as twice the microgram dose of either BDP (18, 19) or BUD (20–23), across a dose range of FP from 200 to 800 \( \mu g \) day\(^{-1} \). At doses of up to 2000 \( \mu g \) day\(^{-1} \) in patients with severe asthma, FP is more effective than an equal dose of BDP (24) or BUD (25). Moreover FP has negligible oral bioavailability, as it is subjected to near-complete first-pass metabolism in the liver (26, 27). This effectively eliminates the oral route for systemic absorption.

In patients with severe asthma, 1500 \( \mu g \) day\(^{-1} \) FP produces no more HPA suppression than an equal dose of BDP (24). A higher FP dose (2000 \( \mu g \) day\(^{-1} \)) produces a greater suppression of serum cortisol than 1600 \( \mu g \) day\(^{-1} \) BUD, but values still remain within the normal range (25). However, a study in healthy adult volunteers has reported that FD produces greater suppression of the HPA axis than BUD over the dose range of 400–2000 \( \mu g \) day\(^{-1} \) administered by metered-dose inhaler (28).

In the above-mentioned studies, the inhalation devices used were metered dose inhalers (MDIs) or Diskhaler. Nowadays, the dry-powder devices Diskus\textsuperscript{TM} (Glaxo Wellcome, London, U.K.) and Turbuhaler\textsuperscript{TM} (Astrazeneca, Lund, Sweden) are most frequently used, at least in Scandinavia (36). The present study was carried out to compare the HPA-suppressing effects of FP (1500 \( \mu g \) day\(^{-1} \)) and BUD (1600 \( \mu g \) day\(^{-1} \)) given via dry-powder inhalation devices (Diskus\textsuperscript{TM} and Turbuhaler\textsuperscript{TM}, respectively) as a primary objective in adult patients with moderate to severe asthma who require these specific high doses of steroid treatment.

### Methods

#### STUDY DESIGN

The study was a randomized, double-blind, double-dummy, cross-over study (Fig. 1). Two treatment periods of 2 weeks each were separated by a 2-week washout period and preceded by a 2-week run-in. Study visits took place prior to run-in, after the run-in period (baseline 1), after the first treatment period, after the washout period (baseline 2) and after the second treatment period.

During the run-in and washout periods, patients received their usual medication for reversible obstructive airways disease, which could include inhaled corticosteroids (BDP or BUD), oral xanthine derivatives, sodium cromoglycate, long-acting \( \beta_2 \)-agonists, anti-histamines, inhaled cholinergics and oral \( \beta_2 \)-agonists. All medication doses were held constant throughout the study. The same inhaled corticosteroid was used during the run-in and washout periods. Compliance was checked by counting doses left over on the Diskus\textsuperscript{TM}.

During the two treatment periods, the patients’ usual inhaled corticosteroid was replaced by study medication. This was either FD 750 \( \mu g \) twice daily via the Diskus\textsuperscript{TM} dry powder inhaler or BUD 800 \( \mu g \) twice daily via the Turbuhaler\textsuperscript{TM}, each with a matching placebo to maintain study blinding. Patients were randomized to receive either FD or BUD for the first treatment period, and then switched to the other for the second treatment period. Short-acting \( \beta_2 \)-agonists, salbutamol or terbutaline, were permitted as rescue medication throughout the study.

The study was conducted in accordance with the Declaration of Helsinki (Hong Kong Amendment 1989), and was approved by the regional Ethical Committee in each country. All patients gave written informed consent for study participation.

#### PATIENTS

Patients were aged 18 to 75 years, with a clinical history of reversible obstructive airways disease responding to inhaled corticosteroids. All patients had been receiving inhaled corticosteroids for at least the last 3 months, and BUD (1600 \( \mu g \) day\(^{-1} \)) or BDP (1500–1600 \( \mu g \) day\(^{-1} \)) at a constant dose for 4 weeks prior to randomization at Visit 1. They were required to demonstrate correct use of the Diskus\textsuperscript{TM} and Turbuhaler\textsuperscript{TM} devices and a peak flow meter. Forced expiratory volume in 1 sec (FEV\textsubscript{1}) was measured at Visits 1 and 2 and was required to be 50% or more of the predicted value on each occasion. All patients had to show a clear response to bronchodilator therapy. This was defined by comparing the peak expiratory flow (PEF) value obtained before inhaling any bronchodilator with the PEF obtained after inhalation of salbutamol. The mean morning PEF obtained before taking any medication on each of the last 7 days of the run-in period could be no more than 90% of the PEF obtained after inhalation of 400–800 \( \mu g \) salbutamol at Visit 2. Patients must also have experienced asthma symptoms (total diary card score of at
least two per 24 h), or have used a short-acting \( \beta_2 \)-agonist on at least two occasions per 24 h, on at least 4 days during the run-in period. These selection criteria defined a patient group with moderate to severe symptomatic reversible obstructive airways disease.

Patients were excluded from the study for the following reasons: very poorly controlled asthma or chronic obstructive pulmonary disease; use of oral, parenteral or depot corticosteroids in the 4 weeks preceding Visit 1; pregnancy (or likelihood of becoming pregnant) or lactation in women; evidence of alcohol or drug abuse; known or suspected hypersensitivity to inhaled steroids; respiratory tract infection or hospitalization for respiratory disease in the 4 weeks prior to Visit 1; night shift work; evidence of serious uncontrolled systemic, psychological or other disease likely to interfere with the conduct of the study.

ASSESSMENTS

The primary efficacy variables were morning serum cortisol measured over the period from 08:00 to 10:30 hours for calculation of area under the curve (AUC), and 12-h nocturnal urinary cortisol excretion. Both these assessments are recognized measures of HPA axis function, and 12-h nocturnal urine cortisol excretion is regarded as the more sensitive of the two (1). Serum samples were taken at 08:00, 08:30, 09:00, 09:30, 10:00 and 10:30 hours at Visits 2, 3, 4 and 5, and urine was collected from 20:00 to 08:00 hours on the nights prior to Visits 2, 3, 4 and 5. Cortisol concentrations in serum and urine samples were determined by a central laboratory (CALAB, Sweden).

FEV\(_1\) was measured at each visit using a spirometer and the highest of three measurements recorded. PEF was measured by the patients each morning (between 07:00 and 09:00 hours) and evening (between 19:00 and 21:00 hours) using a peak flow meter, and the highest of three measurements recorded on a diary card. Daytime asthma symptoms were assessed by the patients and recorded on a diary card, using a six-point scale (0 = no symptoms, 1 = symptoms for one short period, 2 = symptoms for two short periods, 3 = symptoms for most of the day but not interfering with normal activities, 4 = symptoms for most of the day which interfered with normal activities, 5 = symptoms for most of the day which prevented performance of normal activities). Nocturnal asthma symptoms were assessed and recorded in a similar manner, using a slightly different scale (0 = no symptoms,
were not formally analysed.

Period to determine patients’ eligibility for the trial and all. These measurements were used only in the run-in period to determine patients’ eligibility for the trial and were not formally analysed.

STATISTICAL ANALYSIS

Forty patients would enable a treatment ratio of less than 0.80 and greater than 1.25 to be detected with 90% power at the 5% significance level. Approximately 60 patients were to be recruited, with the aim of obtaining 40 evaluable patients at the end of the study.

Previously performed cross-over studies showed that a washout period of 2 weeks should be sufficient for cortisol suppression to recover (28, 37, 38). In these studies, the washout period lasted from 3 to 14 days. Our 2-week washout period was therefore considered adequate to eliminate any carry-over effect from the first to the second washout period was therefore considered adequate to

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Categorical variables were described using frequency distributions, and continuous variables were described using the mean and standard deviation (SD).

AUC serum cortisol for the period 08:00–10:30 hours was calculated using the trapezoidal rule. Analysis of covariance (ANCOVA) for cross-over trials (29) at the end of each treatment period (Visits 3 and 5) was performed using the appropriate baseline value (Visits 2 and 4, respectively) as the covariate. Variations in period, study centre and treatment were allowed for in the analysis. To remove between-patient variability, a nested effect of patient and sequence was included in the model. Twelve-hour urine cortisol excretion was similarly compared. A treatment ratio with corresponding one-sample 95% confidence interval (95% CI) was calculated as the ratio between AUC serum cortisol after FD and after BUD. All tests for significance were two-tailed, and a P-value of <0.05 was considered significant. Statistical analysis was conducted using SAS software (SAS Institute, Cary, NC, U.S.A.).

Results

Sixty patients entered the run-in period, of whom 48 met all the eligibility criteria and were randomized to treatment. Forty-five patients completed the study. Demographic information is given in Table 1. The three patients who discontinued treatment all withdrew from the trial because of adverse events while they were receiving BUD (one for pneumonia, one for asthma deterioration, and one because of the medicinal taste of the study treatment).

Before treatment, the mean serum cortisol concentration at 08:00 hours was 389.5 nmol l⁻¹ in the BUD group. The corresponding values after treatment were 391.1 nmol l⁻¹ and 397.4 nmol l⁻¹ respectively. The numbers of patients having serum cortisol values below the normal range were four before treatment with FP and one after treatment with FP. The corresponding numbers before and after treatment with BUD were two and three, respectively. The corresponding numbers for urinary cortisol were 10 and seven for FP, and 11 and 10 for BUD. The effect on mean serum cortisol from 08:00 to 10:30 hours was similar for both treatment periods (Fig. 2).

Table 2 shows mean serum cortisol AUC values by treatment sequence and treatment period. Serum cortisol was not influenced by treatment sequence (P=0.23), and there were no statistically significant differences between FP and BUD (P=0.63) after controlling for baseline values and study centre.

The ratio between the serum cortisol value observed after FP and that observed after BUD was 1.20 (95% CI 0.92–1.47). Two patients, however, exhibited a very sensitive reaction to BUD but not to FP (serum cortisol AUC of 634.5 and 739.0 nmol l⁻¹ after FP, compared with 165.5

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Patients randomized to treatment (n=48)</th>
<th>Patients entering run-in only (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, years</td>
<td>50.0 (14–6)</td>
<td>52.2 (13–5)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>14 (29)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Men</td>
<td>34 (71)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Mean (SD) FEV₁, % of pred.</td>
<td>76.7 (15–9)</td>
<td>74.3 (21–9)</td>
</tr>
<tr>
<td>Duration of reversible obstructive airways disease &gt;15 years, n (%)</td>
<td>29 (60–4)</td>
<td>6 (50–0)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>11 (22–9)</td>
<td>1 (8–3)</td>
</tr>
<tr>
<td>Previous inhaled corticosteroid, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUD 1600 µg day⁻¹</td>
<td>38 (79–2)</td>
<td>10 (83–3)</td>
</tr>
<tr>
<td>BDP 1600 µg day⁻¹</td>
<td>8 (16–7)</td>
<td>2 (16–7)</td>
</tr>
<tr>
<td>BDP 1500 µg day⁻¹</td>
<td>2 (4–1)</td>
<td>0</td>
</tr>
</tbody>
</table>
and 97.8 nmol l⁻¹ after BUD, respectively). Excluding these two patients from the analysis gave a treatment ratio of 0.99 (95% CI 0.92–1.06), clearly indicating that the two drugs had equivalent effects on the HPA axis.

Fig. 3 presents serum cortisol AUC at baselines and each treatment period for individual patients. In agreement with the mean data shown in Table 2, there was no general pattern of suppression by either treatment. The two patients who exhibited high sensitivity to BUD but not FP may be readily identified.

Twelve-hour nocturnal urine cortisol excretion also showed that both treatments had clinically equivalent effects on the HPA axis. Table 3 presents mean nocturnal urinary cortisol excretion by treatment sequence and treatment group. There was no statistically significant difference between FP and BUD (P=0.80) after controlling for baseline values and study centre, and urine cortisol was not influenced by treatment sequence (P=0.30).

Individual patient data for urine cortisol by treatment period confirm the above finding.

Both FP and BUD were well tolerated. A total of 20 patients reported 29 adverse events, of which the majority occurred in the run-in and washout phases (Table 4).

Two patients experienced exacerbations of asthma while receiving BUD treatment, compared to none during FP treatment. The other three adverse events which occurred during BUD treatment were abdominal pains, medicinal taste and pneumonia. Medicinal taste was considered ‘almost certainly’ to be related to the study treatment but the other events were considered to be unrelated to the study treatment. Both the adverse events which occurred on FP treatment (one patient had mild tonsilitis, and one cut off part of a toe) were considered unrelated to the study medication.

In run-in, the following adverse events were reported: three common cold, one each of erysipelas, gastroenteritis, bursitis of knee, hardening inside lower lip, lumbago, mandibular osteitis and influenza.

In the wash-out period, the adverse events reported were: three common cold, and one each of pruritis of vulva, increased coughing, trauma on left foot, fever, cough, low back pain, thoracic pain, headache, rupture of muscle.

**Discussion**

This study found that FP 1500 μg day⁻¹ via the Diskus™ dry powder device and BUD 1600 μg day⁻¹ via the Turbuhaler™ were equivalent in their effects on the HPA axis in patients with moderate to severe asthma. Neither treatment produced significant suppression of morning serum cortisol or 12-h nocturnal urine cortisol.

These findings are in agreement with previous studies in patients with moderate to severe asthma. A 12-month study comparing 1500 μg day⁻¹ FP and an equal dose of BDP found that there were no differences in morning plasma cortisol, urinary free cortisol or response to adrenocorticotropic hormone, and neither treatment showed any evidence of plasma cortisol suppression (24). A shorter, 6-week study in patients with chronic severe asthma compared FP (1000 μg day⁻¹ or 2000 μg day⁻¹) with BUD (1600 μg day⁻¹)⁻¹(25). Neither FP 1000 μg day⁻¹ nor 1600 μg day⁻¹ suppressed mean plasma cortisol below baseline levels, and although FP 2000 μg day⁻¹ did

![Fig. 2. Mean (sd) serum cortisol over the period 08:00–10:30 hours for each study treatment period. sd shown in one direction only for clarity. (–––), FP 1500 μg; (—), BUD 1600 μg.](image-url)

**Table 2. AUC values for serum cortisol by treatment period and treatment sequence**

<table>
<thead>
<tr>
<th>Treatment period</th>
<th>Mean (sd) AUC serum cortisol, nmol l⁻¹</th>
<th>Treatment sequence</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluticasone/budesonide</td>
<td>Budesonide/fluticasone</td>
<td></td>
</tr>
<tr>
<td>Run-in</td>
<td>n=24</td>
<td>n=22</td>
<td>n=46</td>
</tr>
<tr>
<td></td>
<td>792 (286)</td>
<td>773 (288)</td>
<td>783 (284)</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>n=24</td>
<td>n=21</td>
<td>n=45</td>
</tr>
<tr>
<td></td>
<td>815 (295)</td>
<td>746 (234)</td>
<td>783 (268)</td>
</tr>
<tr>
<td>Washout</td>
<td>n=24</td>
<td>n=21</td>
<td>n=45</td>
</tr>
<tr>
<td></td>
<td>793 (290)</td>
<td>777 (237)</td>
<td>786 (264)</td>
</tr>
<tr>
<td>Budesonide</td>
<td>n=24</td>
<td>n=21</td>
<td>n=45</td>
</tr>
<tr>
<td></td>
<td>817 (350)</td>
<td>762 (244)</td>
<td>791 (303)</td>
</tr>
</tbody>
</table>

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Repeat-dose pharmacokinetic studies of 500 healthy volunteers may differ in their handling of FP. Studies in healthy volunteers were twice as high as those in asthmatic patients (24, 25), and the relevance of findings from these high doses. It would have been inappropriate to select these high doses. It would have been inappropriate to select patients on low doses or even steroid-naive patients for the study in order to treat them with high doses which they already being treated with high doses of inhaled steroids, and that this could already have had an effect on the HPA-axis. However, very few patients had values below normal levels, and their disease was not progressing while they were under treatment. Our aim was to investigate the effect on the HPA-axis as a primary endpoint in patients who require these high doses. It would have been inappropriate to select patients on low doses or even steroid-naive patients for the study in order to treat them with high doses which they clinically did not require. The rationale for performing a short-term cross-over study was to let the patients be their own controls.

A study in healthy volunteers has claimed that FP has a greater effect on the HPA axis than budesonide. A 4-day repeat-dose study compared BUD (200 μg, 400 μg and 1000 μg twice daily) with FP (200 μg, 375 μg and 1000 μg twice daily) and reported that 24-h pooled plasma cortisol levels were significantly lower during FP than BUD treatment at all dose levels (28). This was also shown in a cross-over study with 12 mild asthmatics using high doses of FP and BUD inhaled via a MDI (35). These results are at variance with the results of much larger and longer-term clinical studies in asthmatic patients (24, 25), and the relevance of studies in healthy volunteers to patients with moderate to severe asthma has been questioned (1).

There is some evidence that patients with asthma and healthy volunteers may differ in their handling of FP. Repeat-dose pharmacokinetic studies of 500 μg FP given twice daily found that plasma FP concentrations at steady state in healthy volunteers were twice as high as those in patients with asthma (31, 32). It appears that healthy volunteers absorb more of an inhaled corticosteroid dose from the lung than asthmatic patients, possibly because of differences in airway patency (33). This raises further doubts over the validity of healthy volunteer studies as a method of assessing the probable systemic side-effects of inhaled corticosteroids.

This study could be criticized in that the patients were already being treated with high doses of inhaled steroids, and that this could already have had an effect on the HPA-axis. However, very few patients had values below normal levels, and their disease was not progressing while they were under treatment. Our aim was to investigate the effect on the HPA-axis as a primary endpoint in patients who require these high doses. It would have been inappropriate to select patients on low doses or even steroid-naive patients for the study in order to treat them with high doses which they clinically did not require. The rationale for performing a short-term cross-over study was to let the patients be their own controls.

It may also be put forward that this study does not provide any new information in addition to that from previously performed studies. As the devices used in previous mentioned studies are mostly MDIs, we felt that it was important to investigate the effect on the HPA-axis using dry powder devices such as the DiskusTM and TurbuhalerTM, as these are the most commonly used inhalation devices in clinical practice in Scandinavia today.

A meta-analysis of 14 clinical studies has reported that FP is at least as effective as twice the microgram dose of BUD and BDP, over the dose range of 200–1000 μg day⁻¹ FP (30), and more effective in equal doses (24,25). Recently, it has been reported that FP 1500 μg day⁻¹ has a greater oral steroid-sparing effect than BUD 1600 μg day⁻¹ in chronic severe asthma (34). Taking this evidence of greater efficacy at equal doses in conjunction with the present study’s confirmation of equivalent systemic activity at almost equal doses in asthmatic patients, it appears that FP may have a better therapeutic ratio than BUD. FP offers the potential for improved disease control in patients

| Table 3. Twelve-hour nocturnal urine cortisol by treatment period and treatment sequence |
|--------------------------------------|-------------------|-------------------|
| Treatment period                   | Fluticasone/budesonide | Budesonide/fluticasone | Overall |
|-------------------------------------|------------------------|------------------------|
|                                     | n=23                   | n=23                   | n=46     |
| Run-in                              | 76.8 (30.5)            | 85.9 (58.0)            | 81.4 (46.1) |
| Fluticasone                         | n=24                   | n=21                   | n=45     |
|                                     | 75.4 (43.2)            | 67.7 (34.1)            | 71.8 (39.0) |
| Washout                             | n=24                   | n=21                   | n=45     |
|                                     | 75.3 (39.2)            | 60.5 (33.5)            | 68.4 (37.0) |
| Budesonide                          | n=23                   | n=20                   | n=43     |
|                                     | 62.0 (31.2)            | 69.7 (44.5)            | 65.6 (37.6) |

<p>| Table 4. Adverse events (AEs) by treatment period |
|--------------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Treatment period</th>
<th>Patients experiencing AEs (n)</th>
<th>AEs (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-in</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Washout</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Budesonide</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>29</td>
</tr>
</tbody>
</table>
with moderate to severe asthma, with no increase in systemic side-effects.

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