Formoterol (Foradil®) and medium-high doses of inhaled corticosteroids are more effective than high doses of corticosteroids in moderate-to-severe asthma

C. Mitchella, C. Jenkinsb, R. Scicchitanoc, A. Rubinfeldd, J. Kottakis*c,*

aPrincess Alexandra Hospital, Woolloongabba Queensland, and the University of Queensland, Brisbane, Australia
bRoyal Prince Alfred Hospital, Camperdown, Australia
cRoyal Adelaide Hospital, Adelaide, Australia
dDepartment of Respiratory Medicine and University Department of Medicine, Royal Melbourne Hospital, Parkville, Victoria, Australia
eNovartis Horsham Research Centre, Wimblehurst Road, Horsham, West Sussex RH12 5AB, UK

Received 26 September 2002; revised 28 April 2003; accepted 2 May 2003

Abstract

This double-blind, randomised, multi-centre, parallel-group study compared the effect of adding Foradil® (formoterol fumarate) to existing medium-high doses of inhaled corticosteroids (ICS) with that of doubling the dose of ICS in patients with sub-optimally controlled asthma.

After a run-in period, 203 patients with moderate-to-severe asthma who remained symptomatic despite treatment with 500 mg beclomethasone twice daily, were randomised to receive either 12 mg formoterol twice daily (Foradil® Aerolizer®, Novartis) in addition to beclomethasone 500 mg twice daily, or beclomethasone 1000 mg twice daily and placebo for 12 weeks. The primary efficacy variable was mean morning pre-medication peak expiratory flow (PEF) during the last seven days of treatment.

The difference in PEF between treatments was 27.78 l/min in favour of the formoterol/beclomethasone combination (95% CI 13.42, 42.14 l/min, p = 0.0002; intention-to-treat population). Significant differences in the urinary cortisol/creatinine ratio between treatment groups at 12 weeks (p = 0.001) indicated suppression of the hypothalamic-pituitary-adrenal axis in the patients on beclomethasone 1000 mg twice daily.

The addition of formoterol 12 mg twice daily to beclomethasone in patients with asthma who were poorly controlled with beclomethasone 500 mg twice daily was more effective than doubling the ICS dose and resulted in less suppression of the hypothalamic-pituitary-adrenal axis.

q 2003 Elsevier Ltd. All rights reserved.

Keywords: Asthma; Foradil®; Formoterol; Bronchodilator; Inhaled corticosteroids

1. Introduction

Current guidelines for the management of asthma recommend that patients who experience symptoms while receiving low-to-moderate doses of inhaled corticosteroids (ICS) increase their dose of ICS and, if necessary, add a long-acting β2-agonist (LABA) [1]. More recent studies, however, have shown that the addition of LABAs to low or intermediate doses of ICS provides better asthma control than doubling the dose of corticosteroids [2–9]. Formoterol is a LABA which can be distinguished from other agents in this class by its rapid onset of action [10,11]. The Formoterol and Corticosteroid Establishing Therapy (FACET) study compared exacerbation rates in patients treated with budesonide 100 or 400 μg twice daily, alone or in combination with formoterol 12 μg twice daily. The addition of formoterol to low or intermediate doses of budesonide reduced the number of mild and severe asthma exacerbations compared with budesonide alone [3]. Lung function, rescue medication and the number of night-time
awakenings were also improved. A meta-analysis of nine studies has shown similar evidence that the addition of the LABA, salmeterol to a low dose of ICS is superior to doubling the dose of ICS in terms of reduced symptoms, improved lung function, and reduced need for rescue medication [12]. In addition, the concern that adding a LABA to a low dose of ICS might mask the progression of underlying airways inflammation seems to be largely unfounded [13,14]. Thus, the weight of evidence now suggests that patients with mild-to-moderate asthma who are poorly controlled on ICS will derive significant benefit from the addition of a LABA. There is a shortage of information, however, concerning the combination of ICS and LABAs in patients with more severe disease, who are symptomatic despite high doses of ICS. To our knowledge, only one study [15] has compared the efficacy of the addition of salmeterol to beclomethasone dipropionate (BDP) 500 μg twice daily with that of increasing the dose of BDP to 1000 μg twice daily in patients with asthma who remain symptomatic while receiving the lower dose of the ICS. The objective of this current study was to compare the effect of the addition of the LABA formoterol to medium-high doses of ICS with that of doubling the dose of ICS, in patients with poorly-controlled, moderate-to-severe asthma.

2. Material and methods

2.1. Study subjects

Study subjects were outpatients aged 18 years or more who suffered from moderate-to-severe asthma and gave written informed consent. Inclusion criteria required that initial forced expiratory volume in one second (FEV₁) was ≥50% of predicted and increased by 15% or more within 30 min after a β₂-agonist. If there was historical evidence of asthma determined by a reversibility test carried out within one year, this test was not repeated. Patients had to have received treatment with ICS (delivered by a metered dose inhaler) at a constant daily dose of 1000 μg beclomethasone dipropionate or 800 μg budesonide for at least one month before the screening visit. The presence of at least two of the following on at least 2 of the last 7 days of the run-in period was required: waking at least once a night caused by asthma, asthma interfering with daily activities on at least one day, at least 4 puffs of salbutamol rescue medication a day required, or diurnal variation in peak expiratory flow (PEF) of at least 15%.

Specific exclusion criteria included: patients who had undergone any change in daily dose of ICS in the previous month, patients who had used a LABA or had received a course of oral corticosteroid in the month before the screening visit, and patients who had experienced problems using the Aerolizer® despite proper instruction.

2.2. Study design

This randomised, double-blind, between-patient study was carried out in 16 centres located in Australia and was approved by the appropriate ethics committees at each site. After screening at visit 1, there was an initial run-in period of 2–4 weeks, during which baseline measurements were performed and the patients were treated with beclomethasone dipropionate 500 μg twice daily. Rescue medication with inhaled salbutamol via a pressurised metered dose inhaler (Ventolin®, GlaxoWellcome, 100 μg/puff) was allowed.

Eligible patients were then randomised at visit 2 to receive treatment for 12 weeks with either 2 puffs of beclomethasone dipropionate 250 μg/puff (500 μg) plus 2 puffs of placebo beclomethasone twice daily and formoterol dry powder 12 μg twice daily via the Aerolizer® inhaler (Foradil® Aerolizer®, Novartis) (For/BDP1000 group) or 4 puffs of beclomethasone dipropionate 250 μg/puff (1000 μg) twice daily and placebo formoterol twice daily (P/BDP2000 group). Rescue use of inhaled salbutamol was allowed during the entire treatment period. Short courses of oral corticosteroids (up to 10 days) and/or nebulised β₂-adrenoceptor agonists were allowed for acute asthma exacerbations. Oral β₂-adrenoceptor agonists, anticholinergic drugs, xanthine derivatives and ICS other than trial medication were not allowed. Further examinations were scheduled after 4, 8 and 12 weeks of treatment (visits 3, 4 and 5).

Spirometric measurements were carried out at visit 1, and before dosing at visits 2, 3, 4 and 5. Patients were to abstain from using rescue medication 6 hours before each visit, and the morning dose of study medication was taken after completion of the spirometric measures. All patients kept a daily record of morning and evening peak expiratory flow (PEF), symptom scores during the day and the night, number of inhalations of rescue medication during the day and the night, use of rescue medication within 6 h of measuring PEF, any medication taken in addition to normal treatment, any adverse events and any visits to hospital or doctor for asthma exacerbations.

2.3. Methods

FEV₁ and PEF were measured as previously described [8]. Patients were given instruction on the use of the mini-Wright® peak-flow meter for PEF measurements and study staff at each centre checked its correct usage. On each morning and evening the patients were asked to record in a diary their symptoms on a 0 to 4-point scale [8], where the respective values during the day and night were: 0 = no symptoms; 1 = symptoms waking the patient once, not interfering with daily activity; 2 = noticeable symptoms waking the patient more than once, interfering to some extent with daily activity; 3 = definitely noticeable symptoms waking the patient most nights, interfering greatly
with daily activity; 4 = bad symptoms impairing sleep or daily activity.

Endogenous production of cortisol was determined by measuring the free cortisol concentration in the urine. At visit 2 and at the end of the treatment period, at visit 5, subjects passed urine on waking and then collected their urine for 2 h before taking trial medication. The free fraction of urinary cortisol was measured by extraction (DPC Immulite). Free cortisol concentration was corrected for the creatinine concentration in the urine sample and expressed as a urinary cortisol/creatinine ratio in nmol/mmol [16].

2.4. Analysis

Taking a clinically relevant difference in PEF of 20 l/min would require a sample size of approximately 92 patients per treatment group based on a power of 80 and 5% significance level. Allowing 25% for premature discontinuations increased the sample size to 120 patients per treatment. Therefore, a sample size of 120 patients per treatment group was expected to give sufficient power in this trial.

The primary efficacy variable was mean morning pre-medication PEF during the last 7 days of treatment. Secondary efficacy variables were mean morning pre-medication PEF determined before visits 3 and 4 and mean evening pre-medication PEF values averaged over the last 7 days before each visit; FEV\textsubscript{1} values recorded at visits 3, 4 and 5; asthma symptom scores during the day and at night; number of inhalations of rescue medication taken during the day and at night and, number of asthma exacerbations. An asthma exacerbation was graded as follows: 1. (Mild) asthma symptom score of 3 and increased use of rescue medication; 2. (Moderate) treatment with a course of oral corticosteroids and/or nebulised \(\beta\)-adrenoceptor agonists; 3. (Severe) hospitalisation caused by an asthma exacerbation if the adverse event was considered to be related to the study medication.

For continuous variables, the data were analysed using an analysis of covariance model to test for differences between treatment groups while allowing for any effect of centre, and with the baseline value fitted as a covariate [17,18]. The estimates for the treatment contrast, with the associated 95% confidence intervals (CI), were plotted over time [19]. The other variables were analysed using the van Elteren test [20]. A two-sided 5% level of significance was adopted.

The analysis of efficacy was carried out in the intention-to-treat analysis and, in addition, a confirmatory analysis was carried out on the mean morning pre-medication PEF measured during the last 7 days of treatment in the patients who had completed the whole treatment period. On the basis of previous studies, a difference in mean morning pre-medication PEF of 20 l/min between the treatment groups was considered clinically relevant. The safety analysis population included all the patients who had taken at least one dose of trial medication.

3. Results

3.1. Study subjects

A total of 274 patients were screened for this study and 203 were randomised: 102 to For/BDP1000 and 101 to P/BDP2000. The numbers of patients who completed the entire treatment period were 95 and 89 in the For/BDP1000 and P/BDP2000 groups, respectively. Reasons for discontinuations were adverse events in two patients on For/BDP1000 and four patients on P/BDP2000, failure to meet protocol criteria in two patients on For/BDP1000 and three patients on P/BDP2000, lost to follow-up in three patients on For/BDP1000, withdrawal of consent in two patients on P/BDP2000, unsatisfactory therapeutic effect in one patient on P/BDP2000, non-compliance with treatment in one patient on P/BDP2000, and missing data in one additional patient.

Demographic data and baseline characteristics were comparable in the two treatment groups and are reported in Table 1. The patients studied presented at baseline a mean

<table>
<thead>
<tr>
<th>Variables</th>
<th>For/BDP1000</th>
<th>P/BDP2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>43.9 (14.9)</td>
<td>43.86 (15.4)</td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td>46 (45.1)</td>
<td>44 (43.6)</td>
</tr>
<tr>
<td>Smokers, N (%)</td>
<td>8 (7.8)</td>
<td>10 (9.9)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>49 (48.0)</td>
<td>54 (53.5)</td>
</tr>
<tr>
<td>Previous smokers</td>
<td>45 (44.1)</td>
<td>37 (36.6)</td>
</tr>
<tr>
<td>Disease duration Mean years (SD)</td>
<td>26.5 (15.9)</td>
<td>27.4 (14.7)</td>
</tr>
<tr>
<td>Baseline FEV\textsubscript{1}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean % predicted (SD)</td>
<td>71.83 (11.56)</td>
<td>72.37 (11.16)</td>
</tr>
<tr>
<td>Reversibility, N (%)</td>
<td>53 (52.0)</td>
<td>49 (48.5)</td>
</tr>
<tr>
<td>Current</td>
<td>49 (48.0)</td>
<td>52 (51.5)</td>
</tr>
<tr>
<td>Historical reversibility</td>
<td>25.2 (14.6)</td>
<td>28.4 (16.4)</td>
</tr>
<tr>
<td>Mean % increase in FEV\textsubscript{1} from baseline (SD)</td>
<td>23.8 (8.6)</td>
<td>22.3 (6.4)</td>
</tr>
<tr>
<td>Mean % increase in FEV\textsubscript{1} from baseline (SD)</td>
<td>352.2 (119.8)</td>
<td>349.7 (103.0)</td>
</tr>
<tr>
<td>Mean l/min (SD)</td>
<td>380.4 (122.2)</td>
<td>370.6 (107.9)</td>
</tr>
<tr>
<td>Mean l/min (SD)</td>
<td>1.42 (0.66)</td>
<td>1.44 (0.59)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.69 (0.61)</td>
<td>0.63 (0.61)</td>
</tr>
<tr>
<td>Mean number of inhalations (SD)</td>
<td>3.20 (2.33)</td>
<td>3.32 (2.66)</td>
</tr>
<tr>
<td>Mean number of inhalations (SD)</td>
<td>1.98 (1.71)</td>
<td>1.70 (1.33)</td>
</tr>
</tbody>
</table>

\[\text{a}\] Measured at the screening visit.
\[\text{b}\] Averaged over the last 7 days of the run-in period before visit 2, intention-to-treat population. No significant differences between treatment groups were found (all \(p \geq 0.3\)).
FEV\textsubscript{1} of 72\% of predicted normal value and documented FEV\textsubscript{1} reversibility (27\%) to a standard bronchodilator dose strongly suggestive of asthma; they had moderate symptom scores and required approximately 5 inhalations of bronchodilator per day.

### 3.2. Primary efficacy variable

The mean morning pre-medication PEF during the last 7 days of treatment, in the intention-to-treat population showed a statistically significant difference between treatment groups in favour of For/BDP1000 ($p = 0.0002$) (Table 2). The difference of 27.8 l/min exceeded the limit of 20 l/min considered to be clinically relevant.

These results were confirmed in the population of 178 patients who completed the study, where the difference of 24.8 l/min between treatment groups in favour of For/BDP1000 was again both statistically ($p = 0.0012$) and clinically significant (Table 2).

### 3.3. Secondary efficacy variables

There were significant differences between treatment groups in favour of For/BDP1000 for mean morning pre-medication PEF averaged over the last 7 days before visit 3 and 4 (all $p = 0.0001$) (Fig. 1). Similar results were observed for the mean evening pre-medication PEF averaged over the last 7 days before visits 3, 4 and 5, which was significantly higher in the For/BDP1000 group than in the P/BDP2000 group at all these time points ($p = 0.0031, p = 0.0002$ and $p = 0.0018$, respectively) (Fig. 2).

The mean FEV\textsubscript{1} value before dosing was significantly higher in the For/BDP1000 group than in the P/BDP2000 group at visits 3, 4 and 5 ($p = 0.0011, p = 0.0013$ and $p = 0.0007$, respectively) (Fig. 3).

The mean (± SD) daytime symptom score was significantly lower in the For/BDP1000 group than in the P/BDP2000 group at visit 3 (0.58 ± 0.65 versus 1.07 ± 0.75), visit 4 (0.50 ± 0.57 versus 1.00 ± 0.75) and visit 5 (0.49 ± 0.71 versus 0.99 ± 0.76) (all $p = 0.001$). The percentage of asymptomatic patients in the 7 days before visits 3, 4 and 5 were significantly higher in the For/BDP1000 group than in the P/BDP2000 group ($p = 0.016, p = 0.004$ and $p = 0.001$, respectively) (Fig. 4a). The mean (± SD) night-time asthma symptom score was lower in the For/BDP1000 group than in the P/BDP2000 group at visit 3 (0.32 ± 0.48 versus 0.49 ± 0.56, $p = 0.022$), visit 4 (0.32 ± 0.51 versus 0.46 ± 0.60, $p = 0.018$) and visit 5 (0.34 ± 0.65 versus 0.50 ± 0.57, $p = 0.001$). In the For/BDP1000 group, the percentage of asymptomatic patients during the 7 nights before visits 3, 4 and 5 was higher than in the P/BDP2000 group (Fig. 4b).

The mean (± SD) number of inhalations of rescue medication during the day was significantly lower in the For/BDP1000 group than in the P/BDP2000 group at visits 3 (0.97 ± 1.37 versus 2.62 ± 2.17), 4 (0.90 ± 1.22 versus 2.47 ± 2.40) and 5 (0.93 ± 1.38 versus 2.43 ± 2.43) (all $p = 0.001$). The percentage of patients who did not need daytime rescue medication in the 7 days before visits 3, 4 and 5 was significantly higher in the For/BDP1000 group than in the P/BDP2000 group ($p = 0.011, p = 0.001$ and $p = 0.001$, respectively). The mean (± SD) number of inhalations of rescue medication at night was also significantly lower in the For/BDP1000 group than in the P/BDP2000 group at visits 3 (0.76 ± 1.03 versus 1.63 ± 1.45), 4 (0.69 ± 1.09 versus 1.36 ± 1.34) and 5 (0.69 ± 1.27 versus 1.43 ± 1.56) (all $p = 0.001$). The percentage of patients who did not need night-time rescue medication in the 7 days before visits 3, 4 and 5 was significantly higher in the For/BDP1000 group than in the P/BDP2000 group (all $p = 0.001$).

Thirty-four (34\%) patients in the For/BDP1000 group experienced at least one exacerbation of asthma compared with 51 patients (51\%) in the P/BDP2000 group. Most episodes were grade-1 (mild) exacerbations; only nine patients (9\%) on For/BDP1000 and 12 (12\%) patients on P/BDP2000 experienced grade-2 (moderate) exacerbations.

### Table 2

<table>
<thead>
<tr>
<th>Patients who completed the study, $n = 178$</th>
<th>Intention-to-treat population, $n = 201$</th>
</tr>
</thead>
<tbody>
<tr>
<td>For/BDP1000, $n = 89$</td>
<td>For/BDP1000, $n = 100$</td>
</tr>
<tr>
<td>P/BDP2000, $n = 89$</td>
<td>P/BDP2000, $n = 101$</td>
</tr>
<tr>
<td><strong>Baseline PEF</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>347.4</td>
</tr>
<tr>
<td>SD</td>
<td>123.0</td>
</tr>
<tr>
<td><strong>PEF before visit 5</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>386.7</td>
</tr>
<tr>
<td>SD</td>
<td>130.0</td>
</tr>
<tr>
<td>p value</td>
<td>0.0012</td>
</tr>
<tr>
<td><strong>LS Mean</strong></td>
<td>386.1</td>
</tr>
<tr>
<td>95% CI</td>
<td>375.6, 396.6</td>
</tr>
<tr>
<td><strong>LS Mean difference</strong></td>
<td>24.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>9.9, 39.7</td>
</tr>
<tr>
<td></td>
<td>27.8</td>
</tr>
</tbody>
</table>
P/BDP2000 experienced a grade-2 (moderate) exacerbation. No patient experienced a grade 3 exacerbation in either group, but one patient was admitted to hospital with asthma that was considered unrelated to the study medication and thus according to the protocol, was not graded as a grade 3 exacerbation.

3.4. Safety variables

The number of patients reporting adverse events during the treatment period in each group was 69 (68%) on For/BDP1000 and 71 (70%) on P/BDP2000. The most frequent adverse events were upper respiratory tract infections, headache and worsening asthma. One patient in each treatment group experienced a serious adverse event (bronchial carcinoma on For/BDP1000 and asthma on P/BDP2000) judged as unlikely to be related to the study medication. There were two patients in the For/BDP1000 group and four patients in the P/BDP2000 group who withdrew because of adverse events. In the For/BDP1000 group, the events were chest pain and leg cramps, possibly related to study drug. In the P/BDP2000 group three patients...
Combined therapy with formoterol and beclomethasone was also better than high-dose beclomethasone. The proportion of patients who were symptom-free during the daytime while on combined therapy was more than twice that of the high-dose beclomethasone group at each visit. In addition, the patients receiving combination therapy needed significantly less rescue medication during the day and at night than patients receiving the higher beclomethasone dose. Similarly, the proportion of patients who used no rescue medication on combination therapy was more than twice that of the high-dose beclomethasone group for the daytime use and more than threefold higher for the night-time use at each visit.

Asthma exacerbations were an additional outcome variable in this study. Mild or moderate asthma exacerbations occurred more frequently in the group on the higher dose of beclomethasone than with combination therapy. A larger study with asthma exacerbations as the primary end point is needed to confirm this trend. One patient receiving high-dose beclomethasone was hospitalised for asthma and another had worsening asthma requiring withdrawal from the study. These results are consistent with previous findings in patients with milder asthma, showing that the addition of formoterol to low or intermediate doses of budesonide reduced the number of mild and severe asthma exacerbations compared to budesonide alone [3].

High-dose ICs have been associated with significant systemic adrenal effects [24]. It is proposed that addition of formoterol would allow patients to maintain disease control without the need for higher doses of ICS. In this study, the urinary cortisol/creatinine ratio was significantly lower in the high-dose beclomethasone group than in the combined treatment group after 12 weeks’ treatment, indicating greater suppression of the hypothalamic-pituitary-adrenal axis with high dose beclomethasone. However, as noted in previous studies there was a considerable degree of interindividual variability [24]. These findings also confirm previous observations that doses of beclomethasone dipropionate higher than 1500 μg daily exert a significant suppressive effect on the endogenous release of cortisol [16,25,26].

This study is one of the few studies to document the effects of the addition of a LABA in patients with moderate-to-severe asthma who are already receiving comparatively high doses of ICS. The results mirror those found in milder disease [2–9] and emphasise the benefits, both in terms of efficacy and safety, of the addition of a LABA to an established ICS regimen in patients with poorly-controlled asthma. Because corticosteroids are thought to be associated

### Table 3

Summary of urinary cortisol/creatinine ratios at baseline and at the end of the treatment period (visit 5)

<table>
<thead>
<tr>
<th>Ratio (nmol/mmol)</th>
<th>Baseline</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>For/BDP1000</td>
<td>P/BDP2000</td>
</tr>
<tr>
<td>Mean</td>
<td>50.47</td>
<td>50.02</td>
</tr>
<tr>
<td>SD</td>
<td>32.84</td>
<td>27.18</td>
</tr>
<tr>
<td>p value</td>
<td>0.38</td>
<td>0.001</td>
</tr>
</tbody>
</table>

In this study we have shown that in patients with sub-optimally controlled moderate-to-severe asthma receiving treatment with beclomethasone dipropionate 500 μg twice daily, the addition of formoterol 12 μg twice daily is more effective than doubling the dose of inhaled beclomethasone. The study was designed to reflect current outpatient practice with beclomethasone doses being determined in accordance with local guidelines [21].

Combined therapy with formoterol and beclomethasone significantly improved the objective parameters of airflow obstruction compared with the high-dose beclomethasone treatment. The morning pre-medication PEF during the last 7 days of treatment, which was the primary variable of our study, improved to an extent that was clinically relevant. In addition, the beneficial effect of the addition of formoterol on pulmonary function was evident after 4 weeks of treatment. These results are consistent with previous findings in patients with milder asthma, showing that the addition of formoterol to low or intermediate doses of budesonide reduced the number of mild and severe asthma exacerbations compared to budesonide alone [3].

High-dose ICs have been associated with significant systemic adrenal effects [24]. It is proposed that addition of formoterol would allow patients to maintain disease control without the need for higher doses of ICS. In this study, the urinary cortisol/creatinine ratio was significantly lower in the high-dose beclomethasone group than in the combined treatment group after 12 weeks’ treatment, indicating greater suppression of the hypothalamic-pituitary-adrenal axis with high dose beclomethasone. However, as noted in previous studies there was a considerable degree of interindividual variability [24]. These findings also confirm previous observations that doses of beclomethasone dipropionate higher than 1500 μg daily exert a significant suppressive effect on the endogenous release of cortisol [16,25,26].

This study is one of the few studies to document the effects of the addition of a LABA in patients with moderate-to-severe asthma who are already receiving comparatively high doses of ICS. The results mirror those found in milder disease [2–9] and emphasise the benefits, both in terms of efficacy and safety, of the addition of a LABA to an established ICS regimen in patients with poorly-controlled asthma. Because corticosteroids are thought to be associated

A summary of the urinary cortisol/creatinine ratio results is shown in Table 3. The mean urinary cortisol/creatinine ratio at baseline, when all patients were using the same dose of beclomethasone, was similar in the two treatment groups. At visit 5, there was a statistically significant lower ratio in the P/BDP2000 group than in the For/BDP1000 group (p = 0.001). The mean change in the ratio from baseline to visit 5 was also statistically significantly different between the two groups (p = 0.001), with the patients on For/BDP1000 showing an increase of 3.48 nmol/mmol and the patients on P/BDP2000 showing a reduction of 13.38 nmol/mmol.

### Table 3

Summary of urinary cortisol/creatinine ratios at baseline and at the end of the treatment period (visit 5)

<table>
<thead>
<tr>
<th>Ratio (nmol/mmol)</th>
<th>Baseline</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>For/BDP1000</td>
<td>P/BDP2000</td>
</tr>
<tr>
<td>Mean</td>
<td>50.47</td>
<td>50.02</td>
</tr>
<tr>
<td>SD</td>
<td>32.84</td>
<td>27.18</td>
</tr>
<tr>
<td>p value</td>
<td>0.38</td>
<td>0.001</td>
</tr>
</tbody>
</table>
with a relatively flat dose-response curve, these results are not unexpected; most of the beneficial anti-inflammatory effects of ICS can be achieved at lower doses and thus increasing the dose is unlikely to result in increased efficacy [27,28].

Combination therapy with ICS and LABA allows good asthma management with comparatively low doses of ICS and has led to the introduction of inhaler products that combine fixed doses of the corticosteroid and LABA in the same device. For example, Aubier et al showed that the combination of salmeterol (50 μg) and fluticasone (500 μg) in a single Diskus inhaler twice daily was well tolerated and effective in achieving asthma control in steroid-dependent patients as the separate administration of the two drugs [29]. In a similar study, Ringdal et al compared salmeterol (50 μg) and fluticasone (250 μg) administered via the Diskus inhaler twice daily with formoterol (12 μg) and budesonide (800 μg) administered concurrently by separate Turbuhalers twice daily [30]. They found that the salmeterol-fluticasone combination was significantly superior in terms of reducing asthma exacerbations and night-time symptoms despite the much lower dosage of fluticasone compared with budesonide. Ringdal’s finding, however, is not unexpected because fluticasone is known to be more potent than budesonide [31]. Indeed, a recent meta-analysis found that fluticasone gave small improvements in airway caliber compared to budesonide at half the budesonide dose [32].

Although fixed-dose combination products have been well evaluated and have potential advantages in terms of adherence to treatment and convenience, they do not allow much flexibility for dose adjustment during periods of increased medical need (e.g. during exacerbations) [29,30,33–35]. In contrast, the administration of LABAs and ICSs by separate inhalers allows the dose of each drug to be adjusted according to the patients’ needs and thus offers the potential for more effective implementation of ‘home-based’ asthma management plans. Indeed, a recent study compared fixed-dose combinations of salmeterol (50 μg) and fluticasone (100 or 250 μg) via the Diskus with flexible combinations of formoterol (12 μg) and budesonide (200 or 400 μg) via separate Aerolizer dry powder inhalers, both treatment regimens were administered in the context of a ‘home-based’ asthma management plan. Patients treated with the flexible regimen experienced significantly fewer mild exacerbations compared with those in the fixed-dose group [36]. Clearly, further studies are needed to investigate effective drug delivery and appropriate therapeutic management for optimising the synergistic effect between long-acting β2-agonists and ICS.

In conclusion, this study indicates that the addition of formoterol in patients with moderate-to-severe asthma inadequately controlled by medium-high doses of ICS is a more effective and safer treatment option than increasing the ICS dose.

Acknowledgements

The authors thank the other Australian physicians who contributed patient data: P. Aldons, Prince Charles Hospital, Chermside, Qld; P. Brenmer, Fremantle Hospital, Fremantle WA; D. Bryant, St. Vincent’s Hospital—Sydney, Darlinghurst, NSW; J. Burdon, St. Vincent’s Hospital—Melbourne, Fitzroy, Vic; M. Hayes, Gosford, NSW; S. Morrison, Royal Brisbane Hospital, Herston, Qld; R. Rufin, The Queen Elizabeth Hospital, Woodville, SA; C. Steinfort, Geelong Hospital, Geelong, Vic; J. Streeton, Austin and Repatriation Medical Center, Heidelberg, Vic; F. Thien, Alfred Hospital, Prahran, Vic; P. Thompson, Sir Charles Gairdner Hospital, Nedlands, WA; R. Wood-Baker, Repatriation General Hospital, Battery Point, Tas. This study was sponsored by Novartis Pharmaceutical Australia Pty Ltd.

References

[21] National asthma campaign management handbook, National asthma campaign, South Melbourne, 1996
[22] National asthma campaign management handbook, National asthma campaign, South Melbourne, 1996
学霸图书馆

www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：

图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具