Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma


There is growing evidence that in addition to its bronchodilatory effects, theophylline may be beneficial in the treatment of asthma through anti-inflammatory and immunomodulatory actions [1]. As concluded from a withdrawal study, low-dose theophylline provided further improvement in asthma control in patients already established on high doses of inhaled corticosteroids [2]. In addition, theophylline has been shown to inhibit the late-phase response to an allergen, an effect likely to result from inhibition of allergen-induced airway inflammation [3].

Inhaled corticosteroids are a mainstay of asthma therapy. Current guidelines recommend increasing the dose of the inhaled steroid for patients whose asthma is not well controlled with low-dose inhaled steroids [4]. However, it has recently been shown that addition of long-acting inhaled β₂-agonists instead of higher doses of inhaled steroid may have a more beneficial role in asthma therapy [5, 6]. The aim of the present study was to compare the addition of theophylline to increasing the dose of inhaled steroid in asthmatics who are symptomatic on low-dose inhaled steroid.

Methods

This randomized, double-blind, parallel-group study was designed to examine the efficacy of beclomethasone dipropionate (BDP) 200 µg b.i.d. with added theophylline capsules compared to BDP 400 µg plus matched placebo capsules b.i.d. in patients with mild-to-moderate asthma. The study was conducted between October 1994 and November 1996 in several European countries. Ethics committee approvals were obtained in all countries. The study was conducted in accordance with the Good Clinical Practice Guidelines issued by the European Commission in 1990 and with the Declaration of Helsinki. All patients gave written informed consent.

Patients

All patients showed the cardinal features of asthma and fulfilled the American Thoracic Society criteria for asthma [7]. A total of 229 male and female patients aged 18–70 yrs and not controlled on 400 µg·day⁻¹ BDP or an...
equivalent dose of another corticosteroid were recruited for the study. Entry criteria included: a) body weight of 60–100 kg; a documented reversibility of at least 15% of forced expiratory volume in one second (FEV1) over baseline at 15 min after inhalation of 200 µg salbutamol; FEV1 of 50–85% of predicted normal, and no severe asthma attack or lower respiratory tract infection in the month prior to the trial.

Exclusion criteria were: a history of alcohol and/or drug abuse; participation in another study within 60 days preceding the present study; a current smoker; a history of serious diseases; and concomitant use of oral corticosteroids, oral β-agonists, nedocromil, sodium cromoglycate, ketotifen and long-acting inhaled β-agonists during prospectively defined times prior to randomization.

Study protocol

A screening visit was followed by a run-in period of 1 week to a maximum of 6 weeks, randomization at baseline and a 6 week treatment period.

Screening visit

At screening, the patients underwent the following investigation: medical history, routine physical examination; laboratory work-up, including haematology and biochemistry; pulmonary function test (spirometry); and reversibility test.

Patients were then prescribed a BDP inhaler (100 µg · puff⁻¹) and a spacer device and instructed to take 200 µg b.i.d. during run-in. A salbutamol inhaler was also dispensed and patients were instructed to use this as required.

Patients were issued a diary card and asked to make two entries per day of three peak expiratory flow (PEF) measurements (prior to drug intake), BDP inhalation, salbutamol usage, and symptoms. Symptom scores and salbutamol use recorded in the morning indicate events from the previous night and information recorded in the evening refers to events during the day.

For symptom scores, the following scales were used: 1) Night-time symptoms: 0: none; 1: awake once during the night or in the early morning because of symptoms; 2: awake more than once during the night because of symptoms; 3: awake for a major part of the night because of symptoms; 4: awake for the whole night because of symptoms.

2) Early morning symptoms: 0: none; 1: awoke earlier than usual; 2: awoke once during the night because of symptoms; 3: awoke earlier than usual; 4: very bad symptoms, could not go to work or do usual activities at all.

Baseline and randomization

The run-in period lasted at least 1 week and up to 6 weeks. During this period, the patients were examined once a week. Patients were randomized to treatment if, during the run-in period of at least 1 week, they fulfilled at least one of the following criteria: decrease in morning PEF by $\geq 20\%$ as compared to the value of the previous evening, on $\geq 3$ of the 7 days immediately prior to randomization; nocturnal symptoms on $\geq 3$ nights during the last week, with at least once having a symptom score $\geq 2$: morning symptom score $\geq 2$ on $\geq 3$ days during the last week; daytime symptom score $\geq 2$ on $\geq 3$ days during the last week; $\geq 28$ puffs of salbutamol during the last week.

Patients were randomized to receive either BDP 200 µg b.i.d. plus theophylline 250 mg b.i.d. or BDP 400 µg b.i.d. with matched placebo. Following 250 mg b.i.d. for 1 week, the theophylline maintenance dose was 375 mg b.i.d.

Study visits

Following randomization, the patients returned to the investigational site after 1, 2, 4, and 6 weeks of treatment. At study visits, physical examination and lung function measurements were repeated and asthma exacerbations recorded. An exacerbation of asthma was defined as any worsening of asthma symptoms requiring a change in asthma therapy, other than increased use of rescue medication. Blood samples were taken for determination of the serum theophylline concentration at the final visit. Electrocardiograms (ECGs) were recorded at the beginning and end of the treatment.

All patients were obliged to return all used pop-out sachets and steroid metered-dose inhaler (MDI) devices at the study visit, after 1 week (for capsules), and after 6 weeks (for capsules and MDIs). The consumption of study medication was checked by weighing (MDIs) and counting (capsules). In addition, at each visit the patients were instructed how to use the study medication, especially the MDI with the spacer device. There were no instances of noncompliance among the patients. Throughout the study, patients kept a daily record of their morning and evening PEF (best of three measurements), daytime and night-time symptoms and use of rescue salbutamol.

Drugs and laboratory analysis

Patients were prescribed theophylline (Euphylong®, Byk Gulden, Konstanz, Germany) or matched placebo. Euphylong® has established reproducible and food-independent sustained-release pharmacokinetik properties [8]. BDP was purchased by Glaco (Bad Oldesloe, Germany). Inhalers were of identical appearance in both treatment groups.

Serum theophylline concentrations were determined using a photometric assay (Bayer, Leverkusen, Germany).

Statistical analysis

The primary outcome variable was the improvement in PEF at 6 weeks over baseline. More precisely, the mesor PEF (average of morning and evening PEF) was calculated from diary cards during the respective period prior to
the scheduled visit. As baseline, the values from the week prior to randomization were used. Since both groups received active treatment, it was appropriate to test whether the theophylline/BDP 400 µg·day⁻¹ (test) was at least equivalent to the BDP 800 µg·day⁻¹ (reference). To this end, geometric mean and 95% confidence intervals (95% CI) were calculated for the test/reference ratio of baseline-adjusted population medians. At least equivalence was concluded if the lower limit of the 95% CI was above the equivalence acceptance limit of 0.90, which had been chosen in accordance with clinical requirements [9]. The statistical procedure ensured that the risk of incorrectly concluding equivalence was limited to 5% [10]. With the additional assumption of equality of the population medians and a 15% coefficient of variation for the ratio of PEF measurements on week 6/PEF measurements at baseline, a minimum of 52 patients per group resulted in 80% statistical power for showing at least equivalence [11].

Time courses of lung function variables (PEF, FEV₁) are presented as mean±SD. In view of the add-on treatment in both groups, a one-sided approach appeared to be justified for the secondary comparisons at the four visits within a treatment group. These were done by the one-sided paired t-test. In case of percentage change, a logarithmic transformation of the data was performed. Due to multiple testing, the Bonferroni-Holm correction was applied [12].

Other response variables from the diary card such as asthma symptoms or number of salbutamol puffs during the respective periods were also averaged between scheduled visits, and characterized by the median. Pre-/post-comparisons within a treatment group were conducted with the one-sided Wilcoxon matched pairs signed rank test, while the comparison between treatment was conducted with the two-sided Mann-Whitney U-Test; α=0.05 was considered as relevant. Therefore, a p-value of less than or equal to 0.05 was considered significant.

Results

Of the 229 patients recruited, 190 were randomized to treatment. One hundred patients were randomized to theophylline plus BDP 400 µg·day⁻¹ and 90 patients to BDP 800 µg·day⁻¹. The main reason for withdrawal prior to randomization was ineligibility. After randomization, seven patients were withdrawn due to adverse events (six from the theophylline/BDP group and one from the BDP 800 µg·day⁻¹ group), and one from the theophylline/BDP group due to exacerbation of asthma. The other 49 withdrawals were due to: violation of inclusion criteria (n=37); non-medical reasons (n=10); and medical reasons (n=2). Withdrawals were evenly distributed between the two treatment groups. Sixty nine patients in the theophylline/BDP group and 64 patients in the BDP 800 µg group completed the study according to the protocol and had valid measurements of the primary variable at baseline and week 6. These data were used in the efficacy analysis on a per-protocol and keypoint-available basis. In addition, an intention-to-treat analysis was performed (data not shown, with the exception of the adverse events), which gave nearly identical results and confirmed the statistical conclusions derived from per-protocol analysis.

The groups were well matched for all demographic details (table 1). With respect to the randomization criteria, proportions of patients experiencing nocturnal symptoms, early morning symptoms, daytime symptoms, use of relief medication and PEF variability in the week prior to randomization are summarized in table 2. In the theophylline/BDP group, the serum concentrations of theophylline were 10.1±4.2 mg L⁻¹ (mean±SD).

Home PEF recordings

Mean morning and evening PEF increased from baseline in both groups within the first week of treatment (fig. 1). These increases were statistically significant at all time points even after the Bonferroni-Holm correction (morning: p<0.001, evening: p<0.02). The increases in the theophylline plus BDP 400 µg·day⁻¹ group were generally

Table 1. – Baseline characteristics of the patients in the two treatment groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Theo/BDP 400 µg·day⁻¹</th>
<th>BDP 800 µg·day⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients n</td>
<td>69</td>
<td>64</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>37/32</td>
<td>38/26</td>
</tr>
<tr>
<td>Age yrs</td>
<td>48* (20–70)</td>
<td>49* (18–70)</td>
</tr>
<tr>
<td>FEV₁ L</td>
<td>2.30±0.62</td>
<td>2.40±0.75</td>
</tr>
<tr>
<td>% pred</td>
<td>74±16</td>
<td>76±13</td>
</tr>
<tr>
<td>FEV₁ response salbutamol</td>
<td>28.5±14.6</td>
<td>28.6±15.7</td>
</tr>
<tr>
<td>% change over baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning PEF L·min⁻¹</td>
<td>345±95</td>
<td>344±105</td>
</tr>
<tr>
<td>% pred</td>
<td>(113–540)</td>
<td>(154–550)</td>
</tr>
<tr>
<td>Evening PEF L·min⁻¹</td>
<td>368±106</td>
<td>368±110</td>
</tr>
<tr>
<td>% pred</td>
<td>(110–630)</td>
<td>(168–633)</td>
</tr>
<tr>
<td>Mesor PEF L·min⁻¹</td>
<td>356±99</td>
<td>356±106</td>
</tr>
<tr>
<td>% pred</td>
<td>(111–584)</td>
<td>(162–587)</td>
</tr>
<tr>
<td>PEF variability %</td>
<td>79±20</td>
<td>78±17</td>
</tr>
<tr>
<td></td>
<td>10.1±6.8</td>
<td>10.1±6.3</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD with range in parenthesis. *: median. Theo: theophylline; BDP: beclomethasone dipropionate; M: male; F: female; FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow; Mesor PEF: average of morning and evening PEF; PEF variability: (maximum PEF - minimum PEF)/maximum PEF; % pred: percentage of predicted values.

Table 2. – Randomization criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Š3 nights during the last week with asthma symptoms, with at least once a symptom score Š2</td>
<td>75 (56)</td>
</tr>
<tr>
<td>Morning symptoms score Š2, on Š3 days during the last week</td>
<td>67 (50)</td>
</tr>
<tr>
<td>Daytime symptom score Š2 on Š3 days during the last week</td>
<td>76 (57)</td>
</tr>
<tr>
<td>&gt;28 puffs of salbutamol during the last week</td>
<td></td>
</tr>
<tr>
<td>Decrease in morning PEF by Š20% as compared to the value of the previous evening, on Š3 days during the last week</td>
<td>60 (45)</td>
</tr>
<tr>
<td>PEF: peak expiratory flow.</td>
<td>27 (20)</td>
</tr>
</tbody>
</table>
greater than in the BDP 800 µg·day⁻¹ group. The maximum PEF increases in the theophylline/BDP group were 33 L·min⁻¹ in the morning and 24 L·min⁻¹ in the evening, compared to 22 L·min⁻¹ and 15 L·min⁻¹, respectively, in the BDP 800 µg·day⁻¹ group. Comparison between treatments with regard to the improvement in morning and evening PEF at week 6 showed that theophylline plus BDP 400 µg·day⁻¹ was at least equivalent to BDP 800 µg·day⁻¹ (test/reference ratio: 1.02 and 1.03, respectively; one-sided 95% CI was 0.98 in both cases, clearly exceeding the equivalence acceptance limit of 0.90).

Throughout the study, the median PEF variability improved significantly compared to baseline in both treatment groups. After 6 weeks of treatment, PEF variability was reduced by 29.9% in the BDP 800 µg·day⁻¹ group, and by 31.8% in the theophylline/BDP 400 µg·day⁻¹ group (fig. 2). There was no statistically significant difference between treatments (p=0.960).

Clinical lung function

For both treatment groups, there was an improvement in FEV₁ after 1 week of treatment, which further increased throughout the study (fig. 3). In the theophylline/BDP 400 µg·day⁻¹ group the mean FEV₁ value increased from a baseline of 2.30±0.62 L to 2.56±0.74 L at week 6. In the BDP 800 µg·day⁻¹ group, FEV₁ increased from 2.40±0.75 L to 2.59±0.78 L at the end of treatment period. In the theophylline/BDP 400 µg·day⁻¹ group the increases
in FEV1 were statistically significant at all time points (p<0.009), whereas in the BDP 800 µg·day⁻¹ group the changes were significant after the Bonferroni-Holm correction only at weeks 4 and 6 (p<0.007). Comparison between treatments confirmed equivalence with regard to the improvement in FEV1 at week 6 (test/reference ratio 1.02; one-sided 95% CI 0.97, clearly exceeding the equivalence acceptance limit of 0.90).

Symptoms and use of relief medication

Symptom scores improved significantly in both treatment groups (p<0.001). Compared to the treatment with BDP 400 µg·day⁻¹ in the run-in period, there was a marked reduction of asthma symptoms during the day and the night after 6 weeks of treatment with either theophylline/BDP 400 µg·day⁻¹ or BDP 800 µg·day⁻¹ (fig. 4). There was no statistically significant difference between treatments (day: p=0.575; night: p=0.196).

In accordance with the clinical improvement, daytime and night-time use of relief medication decreased significantly in both treatment groups (fig. 5). There was no statistically significant difference between treatments (day: p=0.392; night: p=0.814).

Adverse events

In general, both treatment regimens were well tolerated. Reporting of adverse events refers to the intention-to-treat group. No serious adverse event was reported. Twenty seven adverse events, which were either pharmacological predictable or attributable to asthma, were observed in the theophylline/BDP group (15 gastro-intestinal symptoms, six palpitations, and six respiratory symptoms such as dyspnoea or cough), and 17 events were observed in the BDP 800 µg group (four gastro-intestinal symptoms, two palpitations, and 11 respiratory symptoms). In addition, a further 23 adverse events in the theophylline/BDP group and 12 events in the BDP 800 µg·day⁻¹ group were reported comprising myalgia, non-respiratory bacterial infections, and weakness.

Discussion

The present study demonstrates clinical equivalence of theophylline plus BDP 400 µg·day⁻¹ compared to BDP 800 µg·day⁻¹ in patients whose asthma is not controlled on BDP 400 µg·day⁻¹. This result supports the use of theophylline as a steroid-sparing agent in the treatment of asthma [1].

The combination of low-dose inhaled corticosteroid and theophylline appears to be intriguing for several rea-
The results of the present study are comparable with those of a recently published abstract [26]. In the latter study, 62 patients were treated for 3 months with theophylline/budesonide 800 µg·day⁻¹ or budesonide 1,600 µg·day⁻¹. The median serum concentration of theophylline was 8.7 mg·L⁻¹. There were greater increases in lung function for the patients treated with theophylline/low-dose budesonide for forced vital capacity (FVC; p=0.03) and FEV₁ (p=0.03). The improvements in β₂-agonist use and PEF variability were comparable in both treatment groups. It is worth noting that low-dose theophylline achieved this without any adverse effect, whereas the higher dose of budesonide was associated with a significant reduction in morning plasma cortisol levels [26]. In the present study, there were more numerous adverse effects in the theophylline-treated group. As is characteristic for theophylline, mild, transient gastrointestinal disturbances were observed more often in the theophylline/BDP 400 µg·day⁻¹ group than in the BDP 800 µg·day⁻¹ group.

The results of this trial and the data from the present study indicate that the combination of inhaled steroid 400–800 µg·day⁻¹ plus theophylline is at least as effective as doubling the dose of inhaled steroids in patients who remain symptomatic on inhaled steroid 400–800 µg·day⁻¹. These effects of theophylline are achievable at serum concentrations in the lower range of the therapeutic window minimizing side-effects [1].

The results of both theophylline/inhaled steroid studies are compatible with trials examining the effects of added salmeterol to inhaled steroid. In these trials with several hundred patients, the addition of salmeterol provided more improvement in lung function and symptom control than did doubling the dose of BDP [5, 6]. Bronchodilatation is the most likely explanation for benefits seen in both salmeterol studies. In contrast to theophylline, there is no evidence for an anti-inflammatory effect of salmeterol. Accordingly, salmeterol plus low-dose inhaled steroid did not reduce PEF variability, as observed for the theophylline/BDP 400 µg·day⁻¹ group in the present study. Additionally, in contrast to the present study, there were no increases in PEF and FEV₁ in the groups of patients treated with high-dose inhaled steroid alone in both salmeterol studies [5, 6].

The addition of theophylline to low-dose inhaled steroid rather than doubling the dose of inhaled steroid is also of importance with respect to the pharmacoeconomics of asthma therapy [27]. Since theophylline is probably the cheapest antiasthma drug available worldwide, the combination of theophylline with low-dose inhaled steroid could lead to considerable savings in expenditure for the management of asthma.

Our study has demonstrated clinical equivalence of theophylline/beclomethasone dipropionate 400 µg·day⁻¹ to beclomethasone dipropionate 800 µg·day⁻¹ in the control of asthma. The addition of theophylline to low-dose inhaled steroid therapy is a suitable alternative to doubling the dose of inhaled steroid for patients with asthma who are not adequately controlled on low-dose inhaled steroid.

Acknowledgements: The authors would like to thank C. Schmid and T. Hummel, for the clinical monitoring and data management, and M. Neuhäuser for valuable comments. The contributions to the study made by the following pneumologists are thankfully acknowledged: Austria: K. Harnoncourt,
References


