Once-daily budesonide in mild asthma

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Inhaled steroid therapy is the most important treatment in the management of chronic asthma and currently twice-daily administration is recommended in mild to moderate asthma. Compliance is often a problem in asymptomatic patients and may lead to reduced disease control.

Our aim was to investigate whether budesonide 0.2 mg once daily administered via the Turbuhaler is as effective as 0.1 mg twice daily.

A randomized, double-blind, parallel group study was carried out in which 76 adult patients with mild to moderate asthma (FEV₁ 86% of predicted) were allocated to budesonide once or twice daily. After a run-in period of 2 weeks on present inhaled steroid treatment (0.2-0.5 mg day⁻¹) there was an 8 week treatment period, followed by a washout period in which patients received no steroid for 4 weeks unless a drop in morning peak flow of at least 20% occurred or the use of β₂-agonists increased by 50%.

Both treatment groups improved minimally in peak flow (1.7 and 4.3 l min⁻¹ in the once-daily and twice-daily groups respectively) but the differences between the two groups were not significant. Testing the reverse hypothesis revealed clinical equivalence. The 90% confidence interval of the difference in the change of peak flow from run-in was between +30 and −30 l min⁻¹, the limits deemed to be clinically relevant. There were no differences in symptom scores, β₂-agonist use or spirometry measurements between the two groups. In the washout period there was a significant deterioration in peak flow and symptoms.

This study shows that 0.2 mg budesonide given once a day is as effective as 0.1 mg given twice daily in patients with mild to moderate asthma.

Introduction

Inhaled corticosteroid therapy is recognized as the most important treatment in the management of chronic asthma (1,2). In severe asthma, a high dosage is necessary but in patients with mild or moderate disease a lower dosage, usually 0.4 mg day⁻¹, is often sufficient.

In mild asthma, patients may be asymptomatic or almost asymptomatic but the inflammatory processes are still present in the airways (3). Thus, regular anti-inflammatory treatment is necessary but in such patients compliance may be a problem. A decrease in the frequency of drug administration is more convenient and can improve compliance in these patients (4). Currently, in moderate asthma twice-daily administration of inhaled steroids is generally recommended but in severe asthma four times daily treatment may be necessary (5,6). One other study showed that in moderate asthma twice-daily dosage of budesonide Turbuhaler was just as effective as four times daily (0.4 mg day⁻¹) (7). However, few studies have investigated a further decrease to once daily. One study showed budesonide inhaled by Turbuhaler (0.4 mg day⁻¹) given in the evening was superior to placebo when used as an initial treatment in mild asthma in patients who had previously received no inhaled steroids (8). Another study showed no difference in the efficacy of once-daily (morning or evening) or twice-daily budesonide inhaled by Turbuhaler (0.4 mg day⁻¹) as initial treatment for asthma (9). Only one recent study showed that in moderate asthma twice-daily budesonide, given via pressurized metered dose inhaler (pMDI), gave better clinical control than a once-daily regimen (0.8 mg day⁻¹), but without significant difference in effect on peak flow (10). A study comparing beclomethasone dipropionate once daily (0.25 mg day⁻¹) with three times daily (0.2-0.3 mg day⁻¹) showed the higher frequency to be superior to the once-daily dosage (11).

Drug deposition in the lungs varies depending on the type of device used and Turbuhaler is capable of delivering double the fraction of respirable drug particles when compared with a pMDI (12,13), thereby facilitating a dose reduction by 50% (14). Therefore, using a daily dose of
0.2 mg budesonide by Turbuhaler may be sufficient in the mild asthmatic patient.

Since there is no general agreement on whether a single daily dose is sufficient as a maintenance treatment in patients with mild to moderate asthma already treated with an inhaled steroid we aimed to investigate whether the efficacy of budesonide, administered via Turbuhaler in a daily dosage of 0.2 mg, is the same when given once or twice daily.

**Method**

**PATIENTS**

Patients aged 18–70 years with a diagnosis of asthma (1,2) currently using an inhaled steroid in a dosage of between 0.2 and 0.5 mg per day, unchanged for at least 2 months prior to study entry, were eligible for inclusion. All patients were recruited from 16 general practices in The Netherlands and monitored during the study by their general practitioner. Other criteria included a prebronchodilator FEV$_1$ above 1 L and a postbronchodilator PEF and FEV$_1$ above 70% of the predicted normal value (15). Patients were excluded if they had had an acute exacerbation of asthma or a lower respiratory tract infection less than 2 months before the start of the study or if they had any significant respiratory or other disease that could affect the study. Women who were pregnant, considering pregnancy or breastfeeding were also excluded. The use of long-acting $\beta_2$-agonists and other inhaled or oral steroids was also precluded.

The permission of the Ethics Commission of Leiden Academic Hospital was obtained. All patients gave written and verbal informed consent.

**STUDY DESIGN**

This was a randomized, double-blind, parallel group study. There was a run-in period of 2 weeks in which patients continued their current steroid treatment. There followed a double-blind treatment period of 8 weeks in which patients were randomly allocated to treatment with budesonide 0.2 mg in the morning and placebo in the evening (once-daily group) or budesonide 0.1 mg twice a day (twice-daily group) administered by Turbuhaler (Astra Draco, Lund, Sweden). Separately labelled morning and evening Turbuhalers were used. The study finished with a steroid-free washout period of 4 weeks during which time the patient’s need for inhaled steroids was assessed. Patients resumed their original inhaled steroids if they had a deterioration in their peak flow of 20% or if a 50% increase of their requirement for inhaled $\beta_2$-agonists over 3 days occurred, relative to the values in the last 14 days in the treatment period. Patients kept a diary twice a day throughout the study and recorded peak flow using the Vitalograph peak flow meter (absolute scale) (Vitalograph, Buckingham, U.K.), asthma symptoms such as wheezing, shortness of breath and cough (score: 0, none; 3, severe) and their requirement for their inhaled $\beta_2$-agonist or ipratropium. In addition, the use of the study drug and any other prescribed medication, the dose and the reason for use was recorded. Patients were told to avoid using inhaled bronchodilators in the 6 h before and to use the medication after the peak flow measurement. Peak flow was measured standing three times and the highest reading recorded. The patient visited the doctor five times during the study approximately every 4 weeks at which time spirometry was performed using a turbine spirometer (Microlab 3300, Sensor Medics, Bilthoven, The Netherlands), the normal values calculated according to the ECCS values (15). Information regarding drug use, symptoms and side-effects was gathered and guidance over the use of the peak flow meter and Turbuhaler was given by the general practitioner. Patients were instructed to fill in the diary completely but primarily honestly. The GPs were instructed and visited regularly by one of us (S.L.C.) to ensure adherence to the protocol.

**STATISTICAL ANALYSIS**

The primary parameter was the mean morning peak flow over the last 14 days of the treatment period. Secondary parameters were the evening diary peak flow, $\beta_2$-agonist use, symptoms score and the (spirometer) peak flow (PEF), FEV$_1$ and FVC (both absolute and as percentage of predicted). The analysis was performed on all randomized patients who had at least eight morning peak flow measurements during the run-in period for comparison with the treatment period. Two-weekly mean data prior to the visits were analysed. All treatment effects except adverse events were estimated by least-squares estimation and tested by two-way lay-out analysis of variance in which centre and treatment were factors. Paired $t$-tests were performed to estimate steroid responsiveness: mean diary data during the last 2 weeks of blind treatment were compared with those during the last 14 days (minimally 7 days) prior to resuming inhaled steroid treatment. For the morning peak flow measurements the reverse hypothesis (that the two treatments are different) was tested and an equivalence analysis was performed. For this we assumed that a difference between treatments of a change in peak flow of at least $30 \text{ L min}^{-1}$ was clinically relevant. It was tested whether the 90% confidence interval did contain this mean value in either direction.

**Results**

Of the 81 patients who took part in the study, 70 completed it and 11 withdrew. Of these 11, five withdrew during the run in period prior to randomization: two withdrawals were due to non-adherence to the protocol, one was due to the development of a serious adverse event (breast cancer) and two chose not to continue with the study. Seventy-six patients were randomized, 38 in each treatment group. Statistical analysis of efficacy was carried out on 71 patients because five patients had not enough baseline peak flow measurements obtained during the run-in period to calculate for (two in the once-daily and three with twice-daily groups). The characteristics of the patients at the start of the study are shown in Table 1.
Table 1. Characteristics of the randomized patients at their inclusion in the study

<table>
<thead>
<tr>
<th></th>
<th>0·2 mg once daily</th>
<th>0·1 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>M:F</td>
<td>18:20</td>
<td>13:25</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41·7</td>
<td>40·3</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>170·3</td>
<td>171·3</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>2·89</td>
<td>2·87</td>
</tr>
<tr>
<td>FFV₁ (% predicted)</td>
<td>86·4</td>
<td>85·7</td>
</tr>
<tr>
<td>PEF (l min⁻¹)</td>
<td>391</td>
<td>394</td>
</tr>
<tr>
<td>PEF (% predicted)</td>
<td>82·1</td>
<td>85·0</td>
</tr>
<tr>
<td>Previously inhaled steroid dose (mg)</td>
<td>0·33</td>
<td>0·36</td>
</tr>
</tbody>
</table>

The demographic data in the two groups were comparable, except that there were more men in the once-daily group. Prior to the study, 52 patients had used beclomethasone dipropionate, 28 budesonide and one used fluticasone propionate.

The primary efficacy parameter was the difference in change or morning peak flow. During the treatment period there was a negligible improvement in peak flow of 1·7 and 4·3 l min⁻¹ in the once- and twice-daily groups respectively (Table 2). Equivalence analysis of these results is shown in Fig. 1. The difference in change in peak flow from run-in between the two groups and the 90% confidence intervals around this difference fall within the 3·0 l min⁻¹ range, i.e. the effects of the treatments can be considered to be equivalent.

The other diary parameters and the other spirometry data are shown in Table 2. None of the differences between the two treatments is statistically significant.

The compliance with study medication intake was calculated from the number of 'clicks' (one click = one dose) remaining in each Turbuhaler after it had been returned at the end of the treatment period and comparing this number with the expected number of 'clicks'. Mean compliance was 100% and 117% for the once-daily and twice-daily group respectively for the morning Turbuhaler and 103% and 113% for the evening Turbuhaler, producing average results of 102% for the once-daily groups and 115% for the twice-daily group. Only 12 patients fell outside the 75–125% range.

Table 2. The change in daily PEF, symptom score, β₂-agonist use and spirometric FEV₁ and PEF during the treatment period

<table>
<thead>
<tr>
<th></th>
<th>0·2 mg once daily</th>
<th></th>
<th>0·1 mg twice daily</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change*</td>
<td>Baseline</td>
<td>Change*</td>
</tr>
<tr>
<td></td>
<td>(mean)</td>
<td>(± SD)</td>
<td>(mean)</td>
<td>(± SD)</td>
</tr>
<tr>
<td>(1) Diary results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning PEF (l min⁻¹)</td>
<td>409</td>
<td>+1·7 ± 57·9</td>
<td>383</td>
<td>+4·3 ± 35·3</td>
</tr>
<tr>
<td>Evening PEF (l min⁻¹)</td>
<td>420</td>
<td>+3·80 ± 51·4</td>
<td>392</td>
<td>+3·3 ± 35·9</td>
</tr>
<tr>
<td>β₂ use (per day)</td>
<td>0·32</td>
<td>+0·02 ± 0·61</td>
<td>0·47</td>
<td>-0·21 ± 0·55</td>
</tr>
<tr>
<td>β₂ use (per night)</td>
<td>0·16</td>
<td>+0·06 ± 0·41</td>
<td>0·17</td>
<td>-0·01 ± 0·24</td>
</tr>
<tr>
<td>Symptoms day (0–3)</td>
<td>0·56</td>
<td>-0·07 ± 0·48</td>
<td>0·62</td>
<td>-0·06 ± 0·60</td>
</tr>
<tr>
<td>Symptoms night (0–3)</td>
<td>0·48</td>
<td>+0·02 ± 0·51</td>
<td>0·50</td>
<td>0·10 ± 0·57</td>
</tr>
<tr>
<td>(2) Spirometry results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>2·89</td>
<td>+0·02 ± 0·24</td>
<td>2·64</td>
<td>+0·03 ± 0·16</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>85·8</td>
<td>+0·19 ± 5·67</td>
<td>80·9</td>
<td>+0·91 ± 4·91</td>
</tr>
<tr>
<td>PEF (l min⁻¹)</td>
<td>413</td>
<td>+10·7 ± 45·8</td>
<td>396</td>
<td>+11·8 ± 29·5</td>
</tr>
<tr>
<td>PEF (% predicted)</td>
<td>86·8</td>
<td>+2·20 ± 9·45</td>
<td>87·3</td>
<td>+2·56 ± 6·68</td>
</tr>
</tbody>
</table>

Baseline: diary parameters measured during the run-in period, spirometry data at randomization (evaluable subjects). Change: diary parameters measured during last 2 weeks on treatment, spirometry data on the visit at week 8. SD: standard deviation.

*None of the differences between the changes is significant at the level \( P < 0·05 \).
The most frequently reported adverse events were symptoms requiring additional treatment (two in each treatment group) and one because of an adverse event, namely hoarseness (twice-daily group). One patient withdrew during the washout period owing to a serious adverse event (breast cancer, twice-daily group). Except for the two cases of breast cancer (one in the run-in period and one in the wash-out period) no serious adverse events were reported. The most frequently reported adverse events were symptoms of common cold and headache. Coughing after inhalation and hoarseness were reported once; oral candidiasis was not observed.

Sixty-eight evaluable patients entered the washout period and, of these, 56 were suitable for statistical analysis (one patient withdrew after discovering breast cancer and 11 patients failed to cease using the inhaled steroid during this period). Of these 56 patients, 23 restarted their inhaled steroid during the washout period, 13 correctly according to the criteria set in the protocol and ten incorrectly. Of the 33 patients who did not restart their steroid, two fulfilled the preset criteria for this restart within 4 weeks, but it is not known when or whether these patients would need to restart inhaled steroids at some time later. Carry-over effect of inhaled steroids may indeed persist during several weeks (17). For the equivalence analysis, we assumed a difference in the change in peak flow of 30 l/min−1 to be clinically relevant. The result of this test indicated that the two treatments can be considered to be equivalent.

In those patients who actually stopped using the inhaled steroid, lung function dropped, symptoms increased and the use of β2-agonist doubled. This indicates that we selected steroid-responsive asthmatic patients. However, within 4 weeks of this washout less than half of these patients restarted their inhaled steroid. The remaining patients did not fulfill the preset criteria for this restart within 4 weeks, but it is not known when or whether these patients would need to restart inhaled steroids at some time later. Carry-over effect of inhaled steroids may indeed persist during several weeks (17). For the equivalence analysis, we assumed a difference in the change in peak flow of 30 l/min−1 to be clinically relevant. The result of this test indicated that the two treatments can be considered to be equivalent.

Since compliance with regular medication particularly in asymptomatic patients is so often a problem it was pleasing to see such a high level of compliance in this study. Few patients took less than 75% of their prescribed medication. Probably, however, compliance was favourably influenced by the fact that the patients had to fill in a diary. It can be expected that a once-daily regimen can yield a better compliance than a twice-daily regimen, but that could not be investigated in the present study, since both groups had to inhale twice daily.

A maintenance dose of 0.4 mg is usually advised for inhaled steroids; we choose a dose of 0.2 mg daily because by Turbuhaler half of the dose can be given (14). Despite lowering the steroid dose from on average 0.34 to exactly 0.2 mg daily no deterioration occurred. This indicates that the patients were (slightly) overtreated in the run-in period and/or confirms the relevance of the two-fold lung function.
deposition figure for Turbuhaler (12,13). From the present data, we do not conclude that all asthmatic patients can be treated with all inhaled steroids once daily. Local pharmacokinetics can be quite different (18). For budesonide, most but not all studies showed that, in patients with moderate to severe asthma, four times daily administration is superior to twice-daily treatment (5–7,19). In cases with mild to moderate disease, not only can the total daily dose be lower (20) but the dosing frequency can apparently be reduced as well (8,9,19,21). Only one study (10) showed long-term asthma control to be inferior during the once-daily budesonide treatment compared with twice-daily treatment, but with equal effect on lung function.

In conclusion, this study confirms the hypothesis that once-daily, low-dose inhaled budesonide can replace twice-daily administration in the successful management of patients with mild asthma. At a dosage of 0.2 mg once daily with mild, well-controlled asthma can be maintained on this regime. This provides general practitioners with extra treatment flexibility in order to provide the therapy most suitable for their patients.

Acknowledgements

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References

7. Nyholm E, Frame MH, Cayton RM. Therapeutic advantage of twice daily over four daily budesonide Turbuhaler compared with placebo as initial prophylactic therapy for asthma. Respir Med 1994; 88: 293–299.