Asthma drug adherence in a long term clinical trial

Gunnar Jónasson, Kai-Håkon Carlsen, Petter Mowinckel

Abstract

Aim—To measure drug adherence in children with mild asthma receiving long term prophylactic treatment.

Methods—Double blind randomised placebo controlled trial. Patients received inhaled budesonide 100 µg or 200 µg daily, or placebo for 27 months. All participants were asked to inhale medication or placebo from two different Turbuhalers (morning and evening) during the study. A total of 122 children (80 boys, 42 girls) aged 7–16 years with mild asthma (mean FEV\textsubscript{1}, 103.7% of predicted) were included in the trial. Drug adherence was assessed by counting the number of remaining doses in the inhaler when study medication was returned at six month intervals.

Results—A statistically significant and continuing decrease in measured drug adherence was found from three to nine months and then to 27 months, reaching mean values of 40.6% and 46.9% for inhaled morning and evening medication respectively. Drug adherence declined more rapidly in the placebo group (compared to active treatment); this difference became significant after two years of treatment. Children aged 9 years or less had better drug adherence during the entire study period, but the difference was only significant for the first three months of the study. Measured drug adherence was significantly higher for evening medication compared to morning medication for all study intervals after nine months.

Conclusion—Measured drug adherence diminishes significantly when treating children with mild asthma in a long term trial. This emphasises the importance of monitoring compliance in clinical trials.

Keywords: drug adherence; patient compliance; inhaled corticosteroids; childhood asthma

Glucocorticoids are the most effective anti-inflammatory drugs in the treatment of asthma and international treatment recommendations currently suggest treating mild persistent childhood asthma with a low dose of inhaled steroids, cromolyn sodium, or nedocromil sodium.\textsuperscript{1} The fact that airway inflammation has been shown to occur in mild intermittent asthma,\textsuperscript{2} may possibly result in prophylactic treatment of a milder form of disease. In the authors’ opinion this will inevitably lead to increased attention on drug adherence in this group of patients.

Drug adherence can be determined directly by repeated measurement of serum concentrations of the drug (or a metabolite) in question, when methods are available (serum theophylline measurements). Treatment adherence can also be indirectly measured objectively by assessing the use or intake of prescribed medication. This has been assessed electronically in a clinical trial concerning the use of inhaled steroids for 13 weeks in childhood asthma and was reported to be 58%.\textsuperscript{3} Few studies have however reported objectively measured drug adherence in a long term trial involving children with asthma. Prescribing prophylactic long term therapy in children with mild asthma in order to treat inflammation in the airways and obtaining symptom control may possibly result in a decline in treatment adherence.

Patients and methods

STUDY DESIGN

The study was a double blind, placebo controlled single centre extension trial. The study was a direct continuation of a previous 12 week trial (n = 163), which has been reported and described in detail elsewhere.\textsuperscript{4} At baseline patients were randomised into four different treatment groups, and each patient received two Turbuhalers, one for morning medication or placebo and the other for evening medication or placebo. Group I patients were given budesonide 100 µg once daily in the morning and placebo in the evening. Group II received budesonide 200 µg once daily in the morning and placebo in the evening. Group III received budesonide 100 µg twice daily. Group IV received placebo twice daily. Clinical assessments were performed at three month intervals during the first year and at six month intervals during the second year.

PATIENTS

A total of 122 children with mild asthma were included in the present study, 80 boys and 42 girls, aged 7–16 years. All were selected from the outpatient clinic at the Section of Allergy and Pulmonology, Department of Paediatrics, Ullevål University Hospital in Oslo. All subjects participated in a two year extension study on the effect of low dose inhaled budesonide on mild asthma, mild being defined as low grade symptoms that did not interfere with sleep and lifestyle, or episodes of cough and wheeze occurring less than once per month.\textsuperscript{5} Table 1 gives demographic details of participants.

METHODS

Patient drug adherence was assessed by counting the remaining doses in the inhaler device which initially contained 200 doses. This was
done at six monthly intervals or when the inhalers were returned. This method has been described in detail elsewhere. If inhalers were lost during the study period, patients were provided with new inhalers for the rest of that six month period, but these patients were excluded from the measurement period.

Drug adherence was calculated as:

\[
\text{% drug adherence} = \frac{200 - \text{number of remaining doses} \times 100}{\text{number of prescribed doses}}
\]

Patients were not informed of compliance measurements and the results of these were unknown to the study investigator until the study was completed. The study was approved by the regional medical ethics committee.

### Statistical Evaluation

Means were used for the index of location and confidence interval as the index of dispersion. Unpaired *t* tests were used to compare drug adherence between different groups, and paired *t* tests were used to compare the difference between morning and evening compliance. Probability values of 0.05 and less were considered to be significant.

### Results

#### Patients

Thirty three patients withdrew during the study period: 19 because of disease deterioration, 14 because of non-compliance, and one because of change of residence. After three months of treatment all inhalers (n = 244) were recovered for measurement from included study subjects. From 9 to 21 months, 94–98% of inhalers of included patients were recovered for measurements, whereas 69% of inhalers (123 of 178) were included in the measurement at the last visit of the study.

#### Drug Adherence Assessment

Mean measured adherence for morning medication dropped significantly (p < 0.05) for twice daily medication: from 76.7% after three months of treatment to 51.7% six months later for morning medication, and respectively from 77.7% to 58.8% for evening medication in the same period. As table 2 shows, mean adherence for twice daily medication continued to diminish throughout the study period. Patients receiving placebo had higher (but not significantly) drug adherence during the first nine months of the study, and thereafter consistently lower adherence when compared to active treatment to the end of the period. This difference was statistically significant during the last six months of the study as shown in table 2.

### Discussion

The present study shows that measured drug adherence in a clinical trial involving children with mild asthma, diminishes significantly with time in a long term study. After nine months of treatment, drug adherence was found to be constantly better in the group of patients that inhaled a low dose of budesonide compared to placebo with significant difference the last six months of the study. Adherence was also found to be significantly better for evening medication at nine months and towards the end of the study. Younger children (7–9 years) had a significantly higher adherence to the inhalation therapy during the first three months of the study, possibly as a result of parental motivation, but this difference seems to be reduced as the adherence decreases.

This study emphasises the importance of monitoring compliance in a clinical trial. This is important with regard to the assessment of a possible dose–response effect of a given treatment; it can also influence the general conclusion to be drawn from a trial, as has been pointed out by others. To the authors’ knowledge, a long term clinical trial, where drug adherence to asthma medication has been objectively measured for more than two years, has not been reported previously.

As with all other indirect measurements of compliance—counting unused blisters or pills, or using an electronic inhaler timer device (Nebulizer Chronolog Forefront Technologies Inc., Lakewood, Colorado, USA)—the method

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**Table 1** Patient characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BUD 100 µg twice daily</th>
<th>BUD 200 µg once daily</th>
<th>BUD 100 µg once daily</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>28</td>
<td>32</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>Boys/girls</td>
<td>18/10</td>
<td>17/15</td>
<td>23/5</td>
<td>22/12</td>
</tr>
<tr>
<td>Age (y)</td>
<td>10.2</td>
<td>10.0</td>
<td>9.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>145.6</td>
<td>145.6</td>
<td>139.3</td>
<td>138.7</td>
</tr>
<tr>
<td>Number of atopics</td>
<td>20</td>
<td>21</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>2.27 (0.57)</td>
<td>2.23 (0.66)</td>
<td>2.30 (0.85)</td>
<td>2.04 (0.67)</td>
</tr>
<tr>
<td>FEV₁ % of pred</td>
<td>106.0 (14.1)</td>
<td>102.1 (11.4)</td>
<td>102.2 (12.8)</td>
<td>104.6 (12.9)</td>
</tr>
<tr>
<td>Reversibility in FEV₁ (%)</td>
<td>4.3 (3.8)</td>
<td>3.6 (3.4)</td>
<td>2.4 (2.8)</td>
<td>3.8 (3.1)</td>
</tr>
<tr>
<td>PEF morning (l/min)</td>
<td>263.8 (62.2)</td>
<td>260.4 (84.2)</td>
<td>259.9 (85.4)</td>
<td>229.5 (75.9)</td>
</tr>
<tr>
<td>Methacholine PD₂₀ (µmol)</td>
<td>3.75</td>
<td>4.33</td>
<td>5.83</td>
<td>4.04</td>
</tr>
<tr>
<td>Maximum fall in FEV₁ (%)</td>
<td>10.6 (8.1)</td>
<td>13.7 (12.4)</td>
<td>14.7 (17.5)</td>
<td>10.1 (9.6)</td>
</tr>
</tbody>
</table>

Results are given as mean (SD).

BUD, budesonide; FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow; PD₂₀, provocative dose causing a 20% fall in FEV₁.
Mean values are given as percentages (95% CI). NS, non-significant.

Table 4 Comparing measured drug adherence between morning and evening doses, when treating mild childhood asthma with inhaled budesonide or placebo for 27 months.

<table>
<thead>
<tr>
<th>Months</th>
<th>Morning</th>
<th>n</th>
<th>Evening</th>
<th>n</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>76.7 (72.2–81.2)</td>
<td>122</td>
<td>77.6 (73.8–81.5)</td>
<td>122</td>
<td>NS</td>
</tr>
<tr>
<td>9</td>
<td>51.7 (46.4–57.0)</td>
<td>115</td>
<td>58.8 (53.6–64.0)</td>
<td>114</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>15</td>
<td>47.7 (41.9–53.5)</td>
<td>103</td>
<td>55.3 (49.4–61.1)</td>
<td>101</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>21</td>
<td>43.6 (37.2–50.0)</td>
<td>93</td>
<td>50.3 (43.4–57.2)</td>
<td>93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>27</td>
<td>40.6 (32.5–48.7)</td>
<td>62</td>
<td>46.9 (38.8–55.0)</td>
<td>61</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Mean values are given as percentages (95% CI). NS, non-significant.

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3500 people with Tourette syndrome

The Tourette Syndrome International Database Consortium began in 1992 as a collaborative project between two centres in Canada and one in the USA, and now collects data from 65 centres in 22 countries on six continents. A recent report (Roger D Freeman and colleagues. Developmental Medicine and Child Neurology 2000;42:436–47) includes information on 3500 people with Tourette syndrome.

There was a preponderance of males at all centres, the overall male:female ratio being 4:3:1. Tics began in all cases before the age of 20, in 41% before 6 years, and in 93% before 10 years. The diagnosis was made before the age of 10 in 56% and before the age of 15 in over 80%. In only 12% of cases was Tourette syndrome the only diagnosis; other diagnoses included attention deficit hyperactivity disorder (60%), obsessive compulsive disorder (27%), obsessive compulsive behaviour (32%), learning disorder (23%), and conduct disorder/oppositional defiant disorder (15%). The number of comorbid disorders (in addition to Tourette syndrome) ranged from none to six (average two) and they strongly influenced the likelihood of behavioural problems—such as, anger control problems, coprolalia, self injury, and sleep difficulties, all of which were much more likely to occur with an increasing number of comorbid diagnoses. Thus, uncontrolled anger occurred in around 5% of those with Tourette syndrome alone, about 40% of those with three additional diagnoses, and over 70% of those with six additional diagnoses.

Behavioural problems in people with Tourette syndrome should lead to renewed assessment for additional psychiatric diagnoses. Treatment of these comorbid conditions may be as important as treatment of the tics (or more important). The existence of this large database should facilitate future research.

ARCHIVIST
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