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Periodic Treatment Regimens With Inhaled Steroids in Asthma or Chronic Obstructive Pulmonary Disease

Is It Possible?

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Objective.—To determine whether inhaled corticosteroids can be discontinued in the stable phase of asthma or chronic obstructive pulmonary disease (COPD) or if this therapy should be continued.

Design.—Nonrandomized open uncontrolled 5-year trial.

Setting.—Prospective study in general practice.

Patients.—Forty-eight patients with steroid-dependent asthma or COPD who had shown a decline in forced expiratory volume in 1 second (FEV₁) of at least 80 mL per year and at least one exacerbation per year during the first 2 years of bronchodilator treatment. Subjects were treated additionally with inhaled steroids for another 2 years and were finally given the option to stop using steroids. Sixteen patients were willing to stop using beclomethasone and were studied for another year. No recruitment bias took place in this consecutive sample in the fifth year of follow-up. Two of 16 patients developed carcinomas and dropped out.

Interventions.—Two years of bronchodilator treatment alone (400 µg of salbutamol or 40 µg of ipratropium bromide four times daily), followed by 2 years of additional inhaled corticosteroid treatment (400 µg of beclomethasone two times daily), and finally 1 year of bronchodilator treatment alone.

Main Outcome Measures.—Decline in lung function (FEV₁), change in bronchial hyperresponsiveness, indicated by a provocative concentration of histamine causing a 20% fall in FEV₁ (PC₂₀), morning peak expiratory flow rate (PEFR), diurnal PEFR, week-to-week variation of PEFR, bronchial symptoms, and exacerbations.

Results.—The course of FEV₁ during the year in which beclomethasone was discontinued was not significantly different when compared with the 2-year period of beclomethasone treatment. Neither did the course of PC₂₀, morning PEFR, diurnal PEFR, symptom score, and exacerbation rate change. Only the week-to-week variation of the PEFR increased after discontinuing steroids.

Conclusions.—Discontinuing inhaled steroids is possible in some patients with asthma or COPD after 2 years of regular treatment. This might indicate that for certain groups of patients with mild asthma or COPD, periodic treatment schedules with inhaled steroids is the treatment policy for the future.

THE CURRENT understanding that inflammation is a major pathophysiologic mechanism underlying asthma¹ and perhaps chronic obstructive pulmonary disease (COPD) as well² has resulted in a shift in treatment policy to the early introduction of inhaled corticosteroids in the international guidelines.²⁻⁴ Several studies⁵⁻¹⁰ have demonstrated that inhaled corticosteroids improve the long-term course of asthma and to a lesser degree of COPD.

Inhaled steroids have already been used for many years. Patient compliance can be a problem, since inhaled steroids do not have a direct symptom-relieving effect and sometimes have side effects such as easy bruising, oral candidiasis, hoarseness or irritation of the oropharynx, osteoporosis, growth retardation in children, or suppression of the adrenal gland. An important question for both physicians and patients is whether treatment with inhaled corticosteroids can be discontinued in a stable phase of the disease or if this therapy should be continued during the rest of the patient's life. In other words, are we really treating the inflammatory processes underlying the disease, or are we only suppressing these processes? Some studies have found that lung function deteriorates after reduction of inhaled steroids,¹¹⁻¹⁰ but two long-term studies reported that after reducing or even stopping inhaled steroids, improvements in lung function could be maintained in some patients.¹⁷,¹⁸ So, although most studies suggest that asthma deteriorates after discontinuing steroids, results of
Table 1.—Summary of Studies Concerning Stopping Inhaled Steroids Published to Date

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Therapy, Duration</th>
<th>Design</th>
<th>Measurements After Stopping Steroids</th>
<th>No. of Dropouts</th>
<th>Results†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vathenen et al†††</td>
<td>20</td>
<td>Budesonide 800 μg, 6 wk</td>
<td>Open, between-patient comparison</td>
<td>2-wk</td>
<td>2</td>
<td>FEV₁ and PD&lt;sub&gt;20&lt;/sub&gt; ↓</td>
</tr>
<tr>
<td>Jenkins and Woolcock‡‡‡</td>
<td>18</td>
<td>Beclomethasone 1200 μg, 3 wk</td>
<td>Open, within-patient comparison</td>
<td>3-wk wash-out period</td>
<td>0</td>
<td>PD&lt;sub&gt;20&lt;/sub&gt; and PEFR ↓</td>
</tr>
<tr>
<td>Bel et al†††</td>
<td>8</td>
<td>Budesonide 800 μg, 4 wk</td>
<td>Open, within-patient comparison</td>
<td>4-wk wash-out period</td>
<td>0</td>
<td>FEV₁ stable</td>
</tr>
<tr>
<td>Kraan et al††‡</td>
<td>17</td>
<td>Budesonide 400 μg, 4 wk</td>
<td>Open, within-patient comparison</td>
<td>4-wk wash-out period</td>
<td>2</td>
<td>FEV₁ ↓</td>
</tr>
</tbody>
</table>

Long-term Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Therapy, Duration</th>
<th>Design</th>
<th>Measurements After Stopping Steroids</th>
<th>No. of Dropouts</th>
<th>Results†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnussen et al†††</td>
<td>16</td>
<td>Steroids, 6 mo</td>
<td>Open, between-patient comparison</td>
<td>6 wk</td>
<td>5</td>
<td>FEV₁ ↓</td>
</tr>
<tr>
<td>Waalikens et al†††</td>
<td>20</td>
<td>Budesonide 800 μg, 2-28 mo</td>
<td>Double-blind, between-patient comparison</td>
<td>4 mo, after 2 mo of reduction</td>
<td>0</td>
<td>FEV₁ and PD&lt;sub&gt;20&lt;/sub&gt; ↓</td>
</tr>
<tr>
<td>Juniper et al††‡</td>
<td>14</td>
<td>Budesonide 400 μg, y</td>
<td>Double-blind, between-patient comparison</td>
<td>3 mo: 6 slopped, 6 halved the dose</td>
<td>0</td>
<td>FEV₁ and PD&lt;sub&gt;20&lt;/sub&gt; stable</td>
</tr>
<tr>
<td>Haahtela et al†††</td>
<td>37</td>
<td>Budesonide 1200 μg, 2 y</td>
<td>Double-blind, between-patient comparison</td>
<td>1 y: half stopped and half tapered off to budesonide 400 μg</td>
<td>5</td>
<td>FEV₁, PEFR, and PD&lt;sub&gt;20&lt;/sub&gt; stable in tapering off group, but on average ↓ in group that stopped Long-term remission in 6 patients who stopped</td>
</tr>
</tbody>
</table>

††FEV<sub>1</sub>, indicates forced expiratory volume in 1 second; PC<sub>20</sub>, provocative concentration of histamine causing a 20% fall in FEV<sub>1</sub>; ↓, decreased; ↑, increased; PEFR, peak expiratory flow rate; diPEFR, diurnal peak expiratory flow rate; and PC<sub>20</sub>, provocative concentration of histamine causing a 15% fall in FEV<sub>1</sub>.

Recent long-term studies indicate that this might not be true for all patients. Table 1 represents a MEDLINE literature search of this subject over the past 12 years.

**HYPOTHESIS**

In controlled studies with inhaled steroids, the lung function improves and stabilizes within 3 to 6 months. The duration of this new level of lung function seems to be stable for individual patients. We hypothesize that periodic treatment with inhaled corticosteroids is possible, at least in individual patients with mild asthma or COPD (Figure).

**EFFECTS OF DISCONTINUING INHALED STEROIDS**

It is not clear how long patients should use inhaled steroids to treat the inflammatory processes underlying the disease. The duration of treatment with steroids in short-term studies did not exceed 6 weeks. It is likely that those studies neither treated the inflammatory processes adequately nor were able to create a stable effect. However, after stopping long-term use of inhaled corticosteroids, a progression of asthma was observed in two studies of patients with moderate-to-severe asthma. The study of Magnussen et al confirmed that the lung function deteriorated when steroids were stopped after they had been used for 6 months. In a study with children who had received steroids for more than 2 years, forced expiratory volume in 1 second (FEV₁), symptom score, and change in bronchial hyperresponsiveness, indicated by a provocative concentration of histamine causing a 20% fall in FEV₁ (PC<sub>20</sub>) deteriorated. These findings were in contrast with the study of Juniper et al of adults with mild asthma. They found that after reducing inhaled steroids (given regularly during 1 year), improvements in responsiveness and lung function could be maintained for at least 3 months. Recently, another study observed that the long-term remission during a 2-year treatment period with 1200 μg of budesonide was maintained well over 1 year in patients treated with a dose that was reduced three times and also in some patients receiving a placebo. Comparable results were observed in our own study. We studied a group of 48 patients with steroid-dependent asthma or COPD. All of these patients had shown a steep decline in FEV₁ of at least 80 mL per year and at least one exacerbation per year during 2 years of bronchodilator treatment. They were treated additionally with 400 μg of beclomethasone two times daily for another 2 years. After 2 years of treatment with inhaled steroids, patients were given the option to stop using steroids. Sixteen patients were willing to stop using budesonethasone. They were studied for another year in an open observational study. The subjects who dropped out did so because of personal reasons unrelated to their disease. Table 2 shows that no recruitment bias took place in this fifth year of follow-up neither at the start nor at 2 to 4 years of the study were clinically (and statistically) significant differences observed between subjects who participated during the fifth year and subjects who did not. The only difference was that subjects who refused to continue this study after 4 years were somewhat younger than subjects who finished this 5-year trial (48 vs 56 years of age at the start of the study), which is not unexpected in the light of this very demanding study. All subjects continued using bronchodilators in the same way as in the previous period (400 μg of salbutamol or 40 μg of ipratropium bromide four times daily). Two of them developed carcinomas and dropped out of the study. The course of FEV₁ of the remaining 14 patients during the year in which beclomethasone was stopped was not significantly different when compared with the 2-year period of beclomethasone treatment (Table 3). Neither did the course of PC<sub>20</sub>, histamine, peak expiratory flow rate (PEFR), diurnal peak expiratory flow rate variation, symptom score, and exacerbation rate change. Only the week-to-week variation of the peak expiratory flow rate increased after discontinuing steroids.

One of the aims of this observational study was to investigate whether there
Comparison of effect of periodic treatment and continuous treatment with inhaled steroids on lung function. Line 1 is based on observations in van Schayck et al, line 2 is based on Dompeling et al, and line 3 represents our hypothesis. FEV₁ indicates forced expiratory volume in 1 second.

Table 2.—Patient Characteristics at the Start of the 5-Year Study, at the Start of Beclomethasone (BDP) Treatment (After 2 Years), and at the Start of the Discontinuation of BDP (After 4 Years)

<table>
<thead>
<tr>
<th>Characteristics†</th>
<th>Dropped Out</th>
<th>Continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of Study No.</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Age, y</td>
<td>48 (1.9)‡</td>
<td>56 (2.3)</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>14</td>
</tr>
<tr>
<td>F</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Smoker</td>
<td>Yes</td>
<td>15</td>
</tr>
<tr>
<td>No</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Allergy</td>
<td>Yes</td>
<td>11</td>
</tr>
<tr>
<td>No</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>2.11 (0.62)</td>
<td>2.02 (0.16)</td>
</tr>
<tr>
<td>FEV₁, % of predicted</td>
<td>59 (3)</td>
<td>65 (4)</td>
</tr>
<tr>
<td>PC₂₀</td>
<td>1.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Reversibility, % of initial</td>
<td>17 (2)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Symptom score</td>
<td>5.3 (0.3)</td>
<td>4.9 (0.4)</td>
</tr>
<tr>
<td>Start of Steroid Treatment (Third Year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, % of predicted</td>
<td>59 (3)</td>
<td>55 (4)</td>
</tr>
<tr>
<td>Start of Discontinuation of Steroid Treatment (Fifth Year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, % of predicted</td>
<td>62 (4)</td>
<td>62 (3)</td>
</tr>
</tbody>
</table>

*Comparisons were made between the group that dropped out of the study after 4 years and the group that continued the study but stopped BDP treatment at the start of the fifth year. Differences between the groups were tested by means of the unpaired Student's t test and Wilcoxon’s test for normally distributed variables, and χ² test for dichotomous variables. Standard error of the mean shown in parentheses. 

†FEV₁ indicates forced expiratory volume in 1 second, and PC₂₀, provocative concentration of histamine causing a 20% fall in FEV₁. 

‡P<.05.

§SPC, expressed as milligrams of histamine per milliliter, is given in geometric means.

<table>
<thead>
<tr>
<th>Yearly Change in Outcome Variable†</th>
<th>0-2 y Before</th>
<th>2-4 y During</th>
<th>4-5 y After</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆FEV₁, mL</td>
<td>−104 (45)</td>
<td>−9 (35)</td>
<td>43 (44)</td>
</tr>
<tr>
<td>∆PC₂₀, doubling dose</td>
<td>0.5 (0.9)</td>
<td>0.3 (0.7)</td>
<td>0.2 (1.1)</td>
</tr>
<tr>
<td>∆PEFR, L/min</td>
<td>−0.7 (2.4)</td>
<td>0.7 (2.0)</td>
<td>−7.5 (3.3)</td>
</tr>
<tr>
<td>∆diPEFR, %</td>
<td>−0.2 (0.2)</td>
<td>−0.3 (0.1)</td>
<td>0.4 (0.5)</td>
</tr>
<tr>
<td>∆covPEFR, %</td>
<td>−0.7 (0.2)</td>
<td>−0.6 (0.3)</td>
<td>0.3 (0.2)</td>
</tr>
<tr>
<td>∆Symptom score, No.</td>
<td>−0.06 (0.02)</td>
<td>−0.004 (0.03)</td>
<td>0.08 (0.07)</td>
</tr>
<tr>
<td>Exacerbation rate, No.</td>
<td>1.3 (0.2)</td>
<td>0.9 (0.3)</td>
<td>0.7 (0.3)</td>
</tr>
</tbody>
</table>

Fourteen patients were treated with a bronchodilator alone during years 0 to 2, treated additionally with beclomethasone 800 μg daily during years 2 to 4, and stopped the inhaled steroid during years 4 to 6. Differences between years 2 to 4 and years 4 to 5 were tested by the paired Student's t test. Standard error of the mean shown in parentheses.

PERIODIC INDIVIDUAL INHALED CORTICOSTEROID REGIMEN

Reducing the dose of an inhaled steroid or even stopping the use of inhaled steroids might be possible in individual patients in a stable phase of the disease. If the dose of steroids is reduced or even discontinued, regular follow-up of patients is necessary to detect a new deterioration in lung function. To detect such a deterioration, regular lung function assessments by either the physician or the patient are required. When a new deterioration in lung function occurs, the treatment regimen with steroids can be raised or restarted for a certain period until a new stable phase has been attained. In this way, lung function can be optimized with the lowest indication of the airway obstruction (16.2% vs 7.1%, P=.08). No other variables (such as smoking behavior, allergy, and the like) could predict an increased decline of FEV₁ after stopping beclomethasone.

This might indicate that the underlying inflammation (indicated by the bronchial hyperresponsiveness) has not yet recovered, while the lung function is already within the normal range. It is not clear whether this indicates that longer steroid treatment is necessary than could be expected on the basis of PEFR measurement and/or symptoms. Further long-term placebo-controlled double-blind studies will have to be performed to assess the optimal duration of treatment with inhaled steroids. It is our hypothesis that in the long run, the prognosis is not worse (or even better) during periodic treatment than during continuous treatment with inhaled steroids. This is illustrated by line 3 in the Figure. This Figure is partly based on observations [line 1, "bronchodilator treatment only," based on van Schayck et al; line 2, "continuous inhaled steroid treatment," based on Dompeling et al] and partly based on hypothetical considerations [line 3, "periodic inhaled steroid treatment"].
If discontinuing inhaled steroids is possible after some time of regular treatment, periodic treatment schedules with inhaled steroids might be the treatment policy for the future for certain groups of patients with mild asthma or COPD. When patients are well instructed by the physicians, individual self-management plans with PEFR measurements taken at home, instructions about when to use inhaled steroids for a specified period of time, and when to consult their physician are within reach. New long-term studies are urgently needed to investigate this possibility.

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