Comparative Safety and Efficacy of Single or Twice Daily Administration of Inhaled Beclomethasone in Moderate Asthma


Objectives: In the treatment of stable mild to moderate asthma, twice-daily administration of inhaled steroids may allow adequate control of the asthma; however, comparisons of the efficacy of once- or twice-daily administration brought contradictory results. This study is a randomized, double-blind crossover trial, set to determine if inhaled beclomethasone dipropionate given once daily in the late afternoon or at bedtime can be as effective as a twice-daily regimen in the treatment of moderate asthma.

Design: Subjects were randomly assigned to 3 different dosing regimens of inhaled beclomethasone: (1) regimen A, a twice-daily dose of 500 μg in the morning and at bedtime; (2) regimen B, a single dose of 1,000 μg in the late afternoon; and (3) regimen C, a single dose of 1,000 μg at bedtime.

Patients and Participants: Enrolled in the study were 42 subjects who required 500 μg of inhaled beclomethasone dipropionate twice daily to control symptoms of asthma and to minimize use of β₂-adrenergic agonists, according to criteria suggested in a recent international consensus on asthma therapy. Prior to receiving therapy with inhaled steroids, all of these patients either had chronic symptoms of asthma that required administration of a short-acting β₂-agonist at least twice per day, or had nocturnal asthma symptoms at least once per week.

Therapy: After a 2-week baseline evaluation, each subject was given the 3 treatment regimens in randomized order, each for a period of 4 weeks. Subjects were asked to record daily symptoms of asthma and peak expiratory flows in the morning and evening. At the end of each treatment period, spirometric data and airway responsiveness to methacholine were measured.

Measurements and Results: Thirty-seven subjects completed the study. No significant difference was found among the 3 treatment regimens for asthma symptoms, FEV₁, the provocative concentration of methacholine causing a 20 percent decrease in the FEV₁ (PC₂₀) (geometric means, 1.41, 1.09, and 1.09 mg/ml), and mean morning and evening peak expiratory flow rates (PEFR). The plasma cortisol level and the adrenocorticotropic hormone (ACTH) response were not significantly different among treatments, nor were side effects, which were minimal.

Conclusion: In moderate asthma controlled with a twice-daily dose of inhaled beclomethasone, a single total daily dose administered in the late afternoon or in the evening provides as good control of asthma for 2 months. (Chest 1994; 105:1732-37)

Inhaled steroids are potent bronchial anti-inflammatory agents.1,2 They are widely used to control asthma when more than occasional inhaled bronchodilators are needed and are helpful in the treatment of mild to moderate exacerbations of asthma.3-7 Furthermore, when taken for prolonged periods, inhaled steroids can decrease airway hyperresponsiveness.8-13 Because asthma is a chronic disease, regular anti-inflammatory therapy is often required to maintain optimal control of asthma symptoms; however, long-term compliance with therapy with inhaled steroids is poor, and administration of a single daily dose of inhaled steroids may improve compliance.14,15

Initially, recommendations for dosing frequency of inhaled steroids were four times daily. Subsequently reports have shown that in mild to moderate asthma, inhaled steroids could be as effective when given twice daily.16-20 Two studies showed that administration of inhaled steroids four times daily offered better control of asthma in severe or unstable asthma.21,22 Three studies have compared daily versus twice-daily doses of inhaled steroids.23-25 McGovern et al26 showed that once-daily therapy seemed less effective, but half of the patients included in this study had severe asthma and required oral steroids regularly. Stiksa et al24 found no difference between twice-daily inhalations and once-daily inhalation. Finally, the other study showed that once-daily therapy given in the morning was less efficient than twice-daily administration.25

Chronopharmacologic studies have shown that the time of administration influences the efficacy of certain drugs.26 Asthma symptoms and airway inflam-
mation may increase at night. Late afternoon or evening administration of antiasthmatic drugs may therefore optimize their effect. In keeping with this hypothesis, once-daily theophylline given in the late afternoon reduces the early-morning decrease in peak expiratory flow rate (PEFR) more efficiently than theophylline administered twice daily. Furthermore, Beam et al recently have shown that administration of prednisone at 3 PM was more effective than an 8 AM or 8 PM dosing to suppress airway inflammation and improve spirometric measurements.

This study is a randomized, double-blind crossover trial, set to determine if inhaled beclomethasone given once daily in the late afternoon or at bedtime can be as effective as a twice-daily regimen to control moderate asthma.

**Materials and Methods**

**Subjects**

Forty-two subjects with moderate asthma were recruited from the Laval Hospital Asthma Clinic. Twenty-three men and 19 women (mean age, 39 years) were diagnosed as having asthma according to the criteria of the American Thoracic Society. All had a greater than 15 percent increase in FEV1 after 200 μg of inhaled albuterol (salbutamol) or had a provocative concentration of methacholine causing a 20 percent decrease in FEV1 (PC20) greater than 8 mg/ml before inhaled steroid therapy was started. To be included in the study, subjects had to have an FEV1 greater than 60 percent of predicted while being treated with inhaled steroids and no increase in respiratory symptoms or in their need for medication in the previous 4 weeks. Subjects who had a symptomatic exposure to allergens or a respiratory infection within the previous month were also excluded. The daily dose of inhaled steroids required for optimal control of asthma had to be at least 1,000 μg of beclomethasone dipropionate or 800 μg of budesonide. The baseline characteristics of the asthmatic subjects are shown in Table 1.

Prior to participating in this study, most of these patients were asked by their own physician to reduce the dose of inhaled steroids. If asthma symptoms flared up, if the use of inhaled β2-agonist increased, or if a 15 percent decrease in PEFR was observed, the patient was told to reincrease the dose of inhaled steroids to the previous level. If the symptoms, PEFR, or inhaled β2-agonist use remained stable, the dose of steroids was kept at this level; however, this reduction in the dose of inhaled steroids was done at least 4 weeks prior to the onset of this study. The reduction was usually done 1 or 3 months after the beginning of therapy with inhaled steroids. The dose of inhaled steroids was determined according to the guidelines established by the Canadian and an international consensus on asthma therapy. To control their symptoms, all subjects used a β2-agonist on demand. Two used a long-acting theophylline preparation, which was kept at the same dosage throughout the study. The protocol of the study was accepted by our local ethics committee, and all subjects signed a consent form.

**Design of Study**

The duration of the study was 14 weeks, including 2 weeks of baseline evaluation, followed by 3 randomized periods of 4 weeks during which inhaled beclomethasone was given blindly at the following dosages: (1) phase A, 500 μg twice daily in the morn-

---

**Table 1—Baseline Characteristics of Asthmatic Subjects**

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>42 (23 M; 19 F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>39 ± 2</td>
</tr>
<tr>
<td>No. with atopy (%)</td>
<td>23 (55)</td>
</tr>
<tr>
<td>Duration of asthma, yr</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>No. with treatment (%)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>β2-receptor agonists</td>
<td>2.4 ± 0.5</td>
</tr>
<tr>
<td>Puffs per day</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Inhaled steroids</td>
<td>2 ± 0.3</td>
</tr>
<tr>
<td>Type of inhaled steroids</td>
<td>26 (67)</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Budesonide</td>
<td></td>
</tr>
<tr>
<td>FEV1, % of predicted</td>
<td>82 ± 2.1</td>
</tr>
<tr>
<td>PEFR, L/min</td>
<td>444 ± 14</td>
</tr>
<tr>
<td>Morning</td>
<td>458 ± 13</td>
</tr>
<tr>
<td>Evening</td>
<td>1.03 (0.07-9.88)</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
**Data Analysis**

The efficacy of the three treatment modes was assessed by comparing the results of FEV₁, morning and evening PEFRs, asthma symptom score, and PC₂₀ methacholine results obtained during the last 2 weeks of each treatment phase. To avoid a carryover effect, only the data from the last 2 weeks of each 4-week treatment period were kept for analysis.

The FEV₁, PC₂₀, inhaled bronchodilator use, and cortisol level were analyzed using a randomized block design. Because more than one variable was being measured, the data were analyzed using multivariate techniques as well.

Analysis of PEFR and asthma symptoms was done using univariate and multivariate techniques with a split-plot design. Nonparametric statistics were used to analyze PEFR values and symptom scores because the distribution of these data was not normal.

**Results**

Forty-two subjects took part in our study. Four had to be withdrawn because of intercurrent exacerbation of their asthma that required oral steroids. Another patient was withdrawn from the study because he had continued to take his baseline medication in addition to the study medication (total of 2,000 μg of beclomethasone per day). One subject was withdrawn during the baseline period, one during the twice-daily treatment, and two during the afternoon single-dose regimen. The final analysis therefore covered 37 subjects who completed the study.

There was no significant difference among the three treatment periods for bronchodilator use. The mean daily number of albuterol inhalations (100 μg per inhalation) was 3.3 puffs per day for phase A, 3.1 puffs for phase B, and 3.3 puffs for phase C (p=0.45).

Symptoms remained minimal throughout the 14 weeks of study, indicating good asthma control with each treatment. No significant difference was found in symptom scores among any of the treatment phases. Mean scores on a scale of 0 to 10 for day and for nighttime respiratory symptoms, respectively (cough, chest tightness, sputum, wheezing, and dyspnea), were as follows: treatment A, 0.3/0.32; treatment B, 0.22/0.21; and treatment C, 0.28/0.31 (p=0.23).

The FEV₁ results at baseline and those at the end of each phase of the study are presented in Figure 1. There was no significant difference among the four measurements. Mean values were 85 percent of the predicted value for phase A, 84 percent for phase B, and 84 percent for phase C (p=0.90).

The mean morning and evening PEFRs did not change significantly throughout the study (Fig. 2). The mean PEFR (AM/PM) was 451/454 L/min for phase A, 441/459 L/min for phase B, and 447/452 L/min for phase C (p=0.81). Diurnal fluctuation in PEFR was minimal (<5 percent) and remained unchanged from baseline to the end of the double-blind phase.

As shown in Figure 3, the PC₂₀ for methacholine was measured at the baseline and at the end of each treatment period. No significant change was found after phases A, B, and C (p=0.51).

Cortisol levels and the response to ACTH remained normal throughout the study period (p=0.23) (Fig. 4). No significant side effect was reported during the study.

At the end of the trial, patients were asked about their preference among the three treatment regimens. Treatment A was favored by nine patients, treatment B by eight, and treatment C by three. Seventeen subjects considered the three treatment regimens to be equally effective.

**Discussion**

This study shows that for stable moderate asthma, a single total daily dose of inhaled beclomethasone at the end of the afternoon or at bedtime provides a
similar control of asthma compared with a twice-daily dose. This is in contrast to prior studies using smaller doses of inhaled beclomethasone in which daily doses were found to be less efficient than twice-daily doses.23,25 These differences may be due to the initial stability of asthma symptoms, which was not determined in some of the previous studies, and the fact that inhaled steroids were given in the morning, as opposed to later during the day, as in our study.

Stiksa et al24 compared the effects of a single morning dose of 800 μg of budesonide to a twice-daily dose of budesonide (400 μg twice a day) and to 200 μg four times a day of beclomethasone dipropionate in 20 asthmatic patients. There was no significant difference among the three groups in terms of symptoms, expiratory flow rates, and β2-agonist use. These authors24 suggested that the efficacy of inhaled steroids increases with the number of daily doses, but that stable asthma could be controlled by a single daily dose.

Many clinical studies have shown that compliance with inhaled steroid therapy is often poor.14,39 Reducing the number of daily inhalations of bronchial anti-inflammatory medication might improve compliance and reduce side effects of inhaled steroids, particularly when required at high doses. In our study, no significant adrenal suppression was seen for the different modes of administration of inhaled steroids, and the incidences of dysphonia and oral candidiasis were similar, however, we did not specifically look at compliance.

The patients included in this study had mild asthma symptoms while receiving inhaled steroids, which means that their asthma was stable. Some may argue that the inhaled dose of steroids received by these patients was too high; however, even while receiving at least 800 μg of inhaled steroids, these subjects continue to daily receive an average of 3.3 puffs of a short acting β2-agonist. According to the international consensus report on the diagnosis and management of asthma,31 subjects are defined as having mild asthma when they used a short-acting inhaled β2-agonist less than three times per week while not receiving any anti-inflammatory drug on a regular basis. Therefore, the patients included in this study had moderate asthma, and in this group of patients, the average dose of 1,000 μg of beclomethasone is often required to maintain good control of asthma symptoms and to keep the need for β2-agonist at a low level. As shown by the study of Spitzer et al,40 even the use of eight puffs per day or more of β2-agonist is associated with an increased risk of death or near death from asthma. This study suggested that the treatment of asthma must rely mainly on anti-inflammatory drugs. In keeping with the recommendations from the recent international consensus, the dose of inhaled steroids must be adjusted to keep the need for inhaled β2-agonist to less than 3 or 4 times per day in moderate asthma and to keep a variation of less than 15 percent in PEFR, which is exactly what we observed in our group of asthmatic patients.31

The mean PC20 of these patients while receiving inhaled steroids was 1.03 mg/ml. Because the chronic use of inhaled steroids often increases the PC20 by at least a threefold change,41 this again confirmed the moderate degree of bronchial hyperresponsiveness of our patients and the need for at least 800 μg of inhaled steroids to achieve optimal control of asthma symptoms.

Progressive withdrawal of steroids has been previously used to assess the need for steroids;16 however, this often causes a destabilization of asthma prior to the beginning of the study. Clinical determination of the minimum inhaled steroid dose was therefore adopted in our study protocol because it has already been used in many studies of this kind. Since the required dose of inhaled steroids had already been adjusted by the attending physician prior to enrollment, we found it to be unnecessary to withhold the treatment for the purpose of our study.
Another potential problem in the interpretation of our results is the relatively short duration of each treatment trial; however, a 1-month treatment with inhaled beclomethasone is usually sufficient to determine whether the drug will succeed in controlling asthma symptoms in moderate asthma. Furthermore, with the randomization procedure, 28 of our subjects were on a single daily dose of beclomethasone for 2 consecutive months without experiencing a deterioration of symptoms or pulmonary function results.

It has been shown that a reduction of inhaled steroids below the minimum required dose to control asthma is associated with an increase in airway responsiveness to agonists. In our study, no significant change in methacholine response was found, suggesting that the steroid dose was sufficient to prevent changes in responsiveness.

A common problem with any negative clinical study is the low statistical power to rule out a β-type error. Our study included 37 subjects and a power of 80 percent to detect a 15 percent difference in peak flow measurements. Previous studies on this topic that included patients with moderate asthma had 12 and 20 subjects. Although it is always preferable to have several subjects, we believe that in our study, any clinically significant change would have been found.

Finally, our results apply to stable, well-controlled asthma. If asthma worsens following an antigenic exposure or a respiratory infection, the dose and probably the number of daily doses would have to be increased to re-establish control of the disease.

In conclusion, for moderate asthma controlled by a twice-a-day dose of inhaled beclomethasone or a single daily dose given in the late afternoon or evening provides a similar level of control. More studies are needed to establish the long-term efficacy of once-a-day inhaled steroid therapy.

ACKNOWLEDGMENTS: We thank Serge Simard for his help with the statistical analysis and Dr. Gaston Labrecque for his help in designing the protocol.

REFERENCES

1 König P. Inhaled corticosteroids: their present and future role in the management of asthma. J Allergy Clin Immunol 1988; 82:297-306
2 Check W, Kaliner M. Pharmacology and pharmacokinetics of topical corticosteroid derivatives used for asthma therapy. Am Rev Respir Dis 1990; 141:S44-51
4 Tukiainen P, Lahdensuo A. Effect of inhaled budesonide on severe steroid dependent asthma. Eur J Respir Dis 1985; 70: 239-44
6 Toogood JH. High-dose inhaled steroid therapy for asthma. J Allergy Clin Immunol 1989; 83:529-36
8 Bhagat RG, Grunstein M. Effect of corticosteroids on bronchial responsiveness to methacholine in asthmatic children. Am Rev Respir Dis 1985; 131:902-06
9 Dutoit J, Salome C, Woolcock AJ. Inhaled corticosteroids reduce the severity of bronchial hyperresponsiveness in asthma but oral theophylline does not. Am Rev Respir Dis 1987; 136:1174-78
10 Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate and beclomethasone dipropionate on allergen induced early asthmatic responses, late asthmatic responses and increased bronchial responsiveness to histamine. J Allergy Clin Immunol 1987; 79:734-40
14 Mayo PH, Richman J, Harris W. Results of a program to reduce admission for adult asthma. Ann Intern Med 1990; 112:864-71
15 Williams H, Verrier ER, Sibert JR. Twice daily versus four times daily treatment with beclomethasone dipropionate in the control of mild childhood asthma. Thorax 1986; 41:602-05
21 Malo JL, Cartier A, Merland N, Ghezzo H, Burek A, Morris J, Jennings BH. Four-times-a-day dosing frequency is better than twice-a-day regimen in subjects requiring a high-dose inhaled steroid, budesonide, to control moderate to severe asthma. Am Rev Respir Dis 1989; 140:624-28
steroids. Eur Respir Dis 1985; 67:254-60
30 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136:225
35 Juniper EF, Frith PA, Hargreave FE. Airway responsiveness to histamine and methacholine: relationship to minimum treatment to control symptoms of asthma. Thorax 1981; 36:575-79