Initial Improvements in Lung Function and Bronchial Hyperresponsiveness Are Maintained During 5 Years of Treatment With Inhaled Beclomethasone Dipropionate and Terbutaline*

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Objectives: Treatment with inhaled corticosteroids reduces bronchial hyperresponsiveness and relieves airways obstruction in patients with asthma. Up to now, it is unknown whether initial improvements are maintained over a long period of time. Therefore, we assessed whether initial improvements in FEV1, provocative concentration of histamine causing a 20% fall in FEV1 (PC20), and peak expiratory flow (PEF) persist with a constant dose of inhaled corticosteroids. Furthermore, we investigated whether FEV1, PC20, PEF indexes, and symptom scores improve after increasing the dose of inhaled corticosteroids in patients who did not respond sufficiently to treatment with beclomethasone dipropionate (BDP), 800 μg/d.

Methods: Sixty-eight patients with bronchial hyperresponsiveness and airways obstruction completed a previous study on 3 years of treatment with terbutaline, 500 μg qid, and BDP, 200 μg qid. Fifty-eight of these patients participated in the current extension of another 2.5 years of follow-up. Every 6 months, FEV1 and PC20 were measured. Five patients dropped out of the study, one for pulmonary reasons. Forty-four patients continued treatment with BDP, 800 μg/d (BDP-800 group), and 9 patients received a higher dose of BDP (500 μg tid; BDP-1,500 group) after the first 3 years because of a rapid decline in FEV1 (> 50 mL/yr) despite BDP treatment during the previous study period.

Results: After the initial improvement, the mean slope of individual regression lines for FEV1, PC20, and morning PEF were -28 mL/yr, -0.01 doubling concentrations per year, and 0.6 L/min/yr, respectively, in the BDP-800 group. In the BDP-1,500 group, there were no statistically significant improvements in FEV1, PC20, PEF indexes, and symptom scores after increasing the dose of BDP.

Conclusions: We conclude that initial improvements in FEV1, PC20, and PEF are well preserved over 5 years in patients with obstructive airways diseases who are treated with terbutaline and BDP. In the patients who responded sufficiently to 800 μg/d of BDP, there was no accelerated decline in FEV1 compared with the general population. Increasing the dose of BDP in a small group of patients with an accelerated fall in FEV1 (initially treated with a moderate dose of BDP) resulted in no significant improvement in FEV1, PC20, PEF indexes, and symptom scores. (CHEST 2002; 121:151–157)

Key words: inhaled corticosteroids; long-term study; obstructive airways disease

Abbreviations: BDP = beclomethasone dipropionate; DC = doubling concentrations; PC20 = provocative concentration of histamine causing a 20% fall in FEV1; PEF = peak expiratory flow

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†A complete list of participants is given in the Appendix.
This study was made possible by grants from the Netherlands’ Health Research Promotion Program and Glaxo. Medication was supplied by Astra Pharmaceuticals, Boehringer Ingelheim, and Glaxo.
Manuscript received October 11, 1999; revision accepted August 15, 2001.
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Many studies have been conducted over the last decade to evaluate treatment effects of inhaled corticosteroids on the course and outcome of asthma and COPD. Effects in asthmatic patients are considerable,1–6 ie, treatment with inhaled corticosteroids improves FEV1, peak expiratory flow (PEF), and symptoms within weeks. Improvements in airways hyperresponsiveness are slower in onset, and gradual amelioration usually continues up to at least 1 year.2 Exacerbation rates are markedly reduced by treatment with inhaled corticosteroids in asthma.2,3,6
Some studies have even indicated that delayed introduction of inhaled corticosteroids in patients with asthma results in an impaired response. In contrast, studies in COPD show less beneficial effects. Thompson et al. showed an improvement in lung function associated with modulation of parameters of airway inflammation, whereas many other short-term studies in patients with COPD showed no benefit. Two long-term studies have suggested an improvement or decreased decline in lung function in some patients with COPD.

Although inhaled corticosteroids have become the mainstay of treatment for patients with asthma and many patients with COPD also receive inhaled corticosteroids, to up to now it is not clear whether initial improvements are maintained over a long period of time. Furthermore, only one study to date has used excessive decline in FEV₁ as criterion for inhaled corticosteroid use in asthma and COPD. We wanted to know whether the conditions of patients who showed excessive decline in FEV₁ notwithstanding treatment with beclomethasone dipropionate (BDP), 800 µg/d, could be improved by doubling the dose of inhaled corticosteroids. Therefore, a group of 58 patients with bronchial hyperresponsiveness and mild-to-moderately severe obstructive airways diseases (asthma and COPD), who had been treated with terbutaline, 500 µg qid, and BDP, 800 µg/d, for a total period of 3 years was treated and followed up for another 2.5 years. The aims of the study were (1) to investigate whether initial improvements would persist on a constant dose of inhaled corticosteroids, and (2) to determine if increasing the dose of inhaled corticosteroids would yield benefit in patients who do not respond sufficiently to initial treatment with moderate doses of inhaled corticosteroids, i.e., those with a decline in FEV₁ (%) during the first 2.5 years of the previous study with BDP, 800 µg/d.

Materials and Methods

The present study (hereafter called the second phase) was a 2.5-year continuation of a previous 3-year evaluation (hereafter called the first phase) of different treatment regimens (β₂-agonist alone or in combination with an inhaled corticosteroid or an anticholinergic agent) in patients with bronchial hyperresponsiveness and moderate-to-severe airways obstruction (asthma and COPD). Two hundred seventy-four patients aged 18 to 60 years were originally included at six university pulmonary outpatient clinics. Inclusion criteria were provocative concentration of histamine causing a 20% fall in FEV₁ (PC₂₀) ≤ 8 mg/mL and FEV₁ > 1.2 L and from 1.64 to 4.5 residual SDs below the predicted value, or the FEV₁/inspiratory vital capacity index < 1.64 residual SDs below the predicted value, provided that total lung capacity was better than 1.64 residual SDs below the predicted value. Prior to randomization, inhaled corticosteroids were withheld for 4 weeks, ketotifen and antihistamines were withheld for 6 weeks, and theophylline was withheld for 2 days. Exclusion criteria were pregnancy, a history of occupational asthma or other serious diseases (e.g., tuberculosis, myocardial infarction, or malignancies), use of oral corticosteroids, β-blockers, nitrates, or anticoagulants, or antibiotics on a maintenance base. One third of all participants were assigned to the treatment arm with β₂-agonists plus inhaled corticosteroids; of these, 68 participants had completed the first phase and were eligible for this second phase. Fifty-eight of these participants were willing to participate.

During the follow-up period of 5.5 years, FEV₁ and PC₂₀ were measured every 6 months. PEF, symptom scores, and the number of extra doses of salbutamol Rotacaps (Gluco) were recorded in diary cards during 14 consecutive days prior to the follow-up visits. Three PEF measurements were performed with a mini-Wright PEF meter (Clement Clarke International; London, UK), in the morning directly after rising, before and 10 minutes after medication, and in the afternoon, before the evening meal. The highest value was recorded and used for analysis. Symptoms of dyspnea, wheeze, cough, and phlegm were recorded separately on a four-point scale (0 = no symptoms, to 3 = severe symptoms).

Study Design

Only subjects who had been treated with terbutaline, 500 µg qid, and BDP, 200 µg qid, during the first phase were invited to participate in this second phase. If the fall in FEV₁ during the first 2.5 years of the first phase had been < 50 mL/yr, they continued on this medication scheme. Subjects with a fall in FEV₁ ≥ 50 mL/yr during the first 2.5 years of the first phase (hereafter called insufficient responders) received a higher dose of BDP (500 µg tid). For relief of symptoms, participants were allowed to use salbutamol, 400 µg, on demand. The inhalation technique was checked at each visit.

Exacerbation

An exacerbation was defined as increased complaints of cough and/or wheezing and/or dyspnea and/or the need of rescue medication in excess of four additional doses of salbutamol, 400 µg, per day, necessitating an oral corticosteroid course of 2 weeks.

Diagnosis

Symptom-based diagnosis groups were made by a standardized medical history, adhering to the criteria of the American Thoracic Society. Patients were categorized as atopic on the basis of skin prick testing.

Lung Function

Spirometry was performed on water-sealed spirometers according to standardized guidelines. Histamine provocation tests were performed using a 2-min tidal breathing method.

Data Analysis

Calculations of PC₂₀ were performed with the base-2 logarithmic transformation as this reflects doubling concentrations (DC) and normalized distributions, and analysis with total serum IgE was performed with the base-10 logarithmic transformation after adding 1 to circumvent the problem of zero values. PEF variability was assessed as mean diurnal variation (out of 14 days) being the absolute value of [(afternoon reading – morning reading)/mean of these two] × 100%. After checking for normality,
Student’s $t$ test was used for parameters with a normal distribution and Mann-Whitney $U$ test for parameters with skewed distributions. $\chi^2$ tests were used for dichotomous variables. Individual regression lines of the FEV$_1$, log$_2$-PC$_{20}$, and PEF values were used to test the slopes before and after increasing the dose of inhaled corticosteroids. Means ($\pm$ SD) are given unless otherwise stated. Analyses were performed using software (SPSS/PC$^+$; SPSS version 4; Chicago, IL; and SAS version 6; SAS Institute; Cary, NC). The study protocol was approved by the medical ethics committees of the participating centers. All patients gave written informed consent.

RESULTS

Fifty-eight of 68 patients were willing to participate in the second phase. These participants were 9.7 years older than the 10 nonparticipants ($p < 0.05$). There were no further statistically significant differences between these groups, especially not with respect to lung function or bronchial hyperresponsiveness. During the second phase, four subjects dropped out for other than pulmonary reasons. One additional patient receiving BDP, 800 $\mu$g/d, had frequent exacerbations and was switched to the higher dose. This patient is left out of the analyses. Nine of the remaining 53 subjects received the increased dose of BDP because of a decline in FEV$_1$ ($> 50$ mL/yr) during the first 2.5 years (the insufficient responders).

Table 1 shows the demographics of the subjects who received a fixed dose of 800 $\mu$g/d (BDP-800 group) throughout the 5.5-year study period and the characteristics of the nine insufficient responders who received BDP, 1,500 $\mu$g/d (BDP-1,500 group) during the second phase. At the beginning of the first phase, there was a higher proportion of current smokers in the BDP-1,500 group than in the BDP-800 group (56% vs 30%) and fewer patients with a symptom-based diagnosis of asthma (11% vs 43%, respectively). There were no statistically significant differences in FEV$_1$, bronchial hyperresponsiveness, PEF recordings, and symptoms between the groups at the start of the first phase (Table 2). During the first phase, the BDP-800 group showed a greater improvement in FEV$_1$ (selection criterion), PC$_{20}$ ($p < 0.05$), and symptom score (significant for changes in dyspnea, wheeze, and phlegm) compared to the BDP-1,500 group.

In the BDP-800 group, within the first half year there was a 7.1% predicted (SD, 12.0% predicted) improvement in FEV$_1$, and it remained stable for the remaining 5 years: mean slope of individual regression lines, $-0.26$% predicted (SD, 1.86% predicted) per year ($-28$ mL/yr [SD, 67 mL/yr$]$). In the BDP-1,500 group, there was a 1.4% predicted (SD, 13.4% predicted) improvement in FEV$_1$ in the first half year. The mean slope during the subsequent 2.5 years of the first phase was $-1.61$% predicted (SD, 4.14% predicted) per year ($-93$ mL/yr [SD, 168 mL/yr$]$). During the second phase, while receiving the increased dose of BDP, the mean slope of these nine patients improved considerably but not significantly to $-0.07$% predicted (SD, 3.10% predicted) per year ($-24$ mL/yr [SD, 110 mL/yr$]$). Figure 1 shows the changes in FEV$_1$ from baseline during the whole study in both groups.

In the BDP-800 group, PC$_{20}$ improved by 1.8 DC (SD, 2.33 DC) after 1 year and remained stable thereafter. The mean slope of PC$_{20}$ after the first year was $-0.01$ DC (SD, 0.46 DC) per year during the remaining 4.5 years. In the BDP-1,500 group, the mean slope of the individual regression lines

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*Data are presented as No. (%) unless otherwise indicated. BDP-800 group = patients with the fixed dose of 800 $\mu$g/d of BDP throughout the 5.5 years of both studies; BDP-1,500 group = patients with 800 $\mu$g/d of BDP in the first 3 years and 1,500 $\mu$g/d of BDP in the last 2.5 years; Symptom score = 4-point scale (0 = no symptoms, to 3 = severe symptoms); ΔSymptom score = symptom score baseline second phase − baseline first phase.

†After 3 years of treatment (terbutaline, 500 $\mu$g qid, and BDP, 200 $\mu$g qid).

$p < 0.05$ between groups.
During the last 2.5 years of the first phase for PC$_{20}$ was $-0.16$ DC (SD, 0.36 DC) per year; during the 2.5 years of the second phase, with the increased dose of BDP, the slope was $+0.30$ DC (SD, 0.89 DC) per year, which was not significantly different ($p = 0.075$). Figure 2 shows the changes in PC$_{20}$ from baseline of both groups.

Within the first half year in the BDP-800 group,
mean morning PEF, evening PEF, and PEF variability improved with 59 L/min (SD, 61 L/min), 40 L/min (SD, 54 L/min), and −6.7% (SD, 11.2%), respectively. The slopes during the following 5 years were 0.6 L/min (SD, 7.9 L/min) per year, −0.4 L/min (SD, 8.0 L/min) per year, and −0.22% (SD, 1.23%) per year, respectively. The slopes of the PEF measurements in the BDP-1,500 group, obtained during the last 2.5 years of the first phase and during the 2.5 years of the second phase, with the increased dose of BDP, changed from −6.5 L/min (SD, 10.6 L/min) to −1.4 L/min (SD, 9.6 L/min) per year for morning PEF, from −10.8 L/min (SD, 12.3 L/min) to −0.4 L/min (SD, 9.6 L/min) per year for evening PEF, and from −0.90% (SD, 1.58%) to −0.02% (SD, 2.33%) per year for PEF variability. These changes were not statistically significant. There was also no statistically significant improvement in symptoms after increasing the dose of inhaled corticosteroids.

**Discussion**

The second phase of this study was an observational one. With the current knowledge on efficacy of these anti-inflammatory drugs, it is not ethical to withhold patients from treatment with inhaled corticosteroids for years on end. The study shows that in patients with bronchial hyperresponsiveness and airways obstruction who respond to treatment with inhaled BDP and terbutaline, initial improvements in FEV1 percent predicted and PC20 were well maintained over an additional period of 5 years. An important observation was that in patients who respond well to inhaled steroids initially, there is no increased decline in FEV1, PEF, and symptoms after increasing the dose of BDP.

Many relatively short-term studies1,3–6 have shown the importance of treatment with inhaled corticosteroids in patients with asthma. Additionally, there is an indication that delayed treatment with inhaled corticosteroids leads to a smaller response in PC20.7,8 However, it is as yet unknown whether improvements in outcome parameters such as PC20 and FEV1 can be maintained when treatment is kept constant. This study shows that patients who respond to inhaled corticosteroids retain the initial improve-
ment in FEV₁ and PC₂₀ up to a follow-up period of 5 years. Current guidelines advocate decreasing the dose of inhaled corticosteroids, if possible, although algorithms about how to do this are currently lacking, as are data to support the feasibility of stepping down the medications. Because the importance of the issue, it needs to be determined in further studies whether the stabilization of FEV₁ and PC₂₀ found in our study with constant dosing of inhaled corticosteroids can also be maintained at lower dosages.

There has been quite a controversy about adverse effects of continuous dosing of β₂-agonists. Our study was not designed to specifically address that issue, but during 5.5 years of four-times-daily dosing of terbutaline, 500 μg, we saw no readily apparent generalized detrimental effects on lung function.

Patients who did not respond sufficiently to BDP, 800 μg, showed no statistically significant improvement in FEV₁, PC₂₀, PEF indexes, and symptoms after increasing the dose of BDP. Because of the small number of patients (n = 9), we cannot draw firm conclusions from the results. Although there was no statistically significant improvement in FEV₁ after increasing the dose of inhaled corticosteroids, there was a trend in improvement. Mean slope of FEV₁ before increasing the dose of BDP was −1.61 and improved to −0.07% predicted per year (−93 mL/yr and −24 mL/yr, respectively). Additionally, there were also trends toward improvement in PEF and PC₂₀, though these trends were nonsignificant, possibly due to the small number of patients. The slopes of the PEF measurements changed from −7 to −1 L/min/yr for morning PEF, from −11 to 0 L/min/yr for evening PEF, and from −0.90 to −0.02%/yr for PEF variability. The slope of PC₂₀ changed from −0.16 to +0.30 DC/yr (p = 0.075). The improvements most likely signify that the lower dose was insufficient to suppress the ongoing inflammation in the airway wall in these patients.

Kerstjens et al have shown that a larger immediate (within 3 months) effect of inhaled corticosteroids on FEV₁ can be predicted independently by lower PC₂₀, not smoking, and higher IgE. In our study, the nonresponsive group did have a higher PC₂₀ and a higher smoking rate (Tables 1, 2), probably at least partially explaining the lack of response. However, this group had a somewhat higher IgE. Additionally, we looked at changes in smoking pattern during the study. During the first 2.5 years, four patients stopped smoking and two other patients restarted, all of them within the responsive group. Therefore, the lack of response is not explained by the change in smoking pattern during the study. In summary, it was not possible to predict nonresponders based on individual baseline characteristics. The clinical characteristics of the patients who did not respond sufficiently would seem to be compatible with COPD, as these patients were older, less hyperresponsive, and fewer patients had never smoked; however, mean reversibility was still 9% predicted (14% initial), mean PEF variation was 15%, and six of nine patients in this group were allergic.

Both clinical and epidemiologic studies have suggested that on average there exists an increased fall in FEV₁ over time in patients with asthma. An important result of our study is the finding that the patients with airways obstruction and bronchial hyperresponsiveness who sufficiently respond to treatment with inhaled corticosteroids did not have an accelerated decline in FEV₁ (mean decline was 28 mL/yr), as the published average decline in the general population is 28 mL/yr, even though those data were derived cross-sectionally. The mean slope of FEV₁ percent predicted, thus taking into account sex, age, and height, was −0.26% predicted per year, which is probably clinically negligible.

This study stresses the importance of continuous long-term treatment with inhaled corticosteroids in patients with bronchial hyperresponsiveness and obstructive airways diseases. Initial improvements in lung function and bronchial hyperresponsiveness are preserved and there is no accelerated fall in FEV₁ compared to values from the general population. In the small group of patients with an accelerated decline in FEV₁ despite treatment with moderate dose of inhaled corticosteroids, higher doses of BDP did not significantly improve lung function, bronchial hyperresponsiveness, and symptoms, though nonsignificant trends toward improvement were seen for every parameter. Further studies are necessary to determine whether (temporarily) decreasing the dose of BDP would be possible without loss of the initial improvements.

**APPENDIX**

The Dutch Chronic Nonspecific Lung Disease Study Group consists of a steering committee (K.F. Kerrebijn, Ph.H. Quanjer, H.J. Sluiter), and members from the Departments of Pulmonology of the University Hospital of Amsterdam (E.M. Pouw, D.F.M.E. Schoonbrood, C.M. Boos, H.M. Jansen), Groningen (P.-L.P. Brand, A. de Gooijer, H.A.M. Kerrebijn, D.S. Postma, J.J. Sluiter), the Juliana Children’s Hospital, the Hague (E.J. Duiverman, J.M. Kouwenberg, H.J. Sluiter), and members from the Departments of Pediatric Pulmonology at the Sophia Children’s Hospital, Rotterdam (E.E.M. van Essen-Zandvliet, K.F. Kerrebijn), the Juliana Children’s Hospital, the Hague (E.J. Duiverman, J.M. Kouwenberg, J.E. Frinsen), University Hospital of Groningen (H.J. Waalkens, J. Gerritsen, K. Knol); from the Department of Allergology,
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