Inhaled budesonide improves the course of asthma and COPD

E. Dompeling*, C.P. van Schayck*, J. Molema**, H. Folgering**, P.M. van Grunsven*, C. van Weel*

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ABSTRACT: The effects of inhaled budesonide dipropionate (BDP), 800 μg daily, on the long-term course of asthma and chronic obstructive pulmonary disease (COPD) were investigated in a prospective, controlled study, over three years. During the first two years, patients were treated with a bronchodilator only (salbutamol or ipratropium bromide). Fifty-six patients (28 asthma, 28 COPD), with an unfavourable course of disease during bronchodilator therapy alone (an annual decline in forced expiratory volume in one second (FEV1) of ≥150 ml·yr⁻¹ in combination with at least one exacerbation yr⁻¹), were selected for additional treatment with inhaled budesonide dipropionate (BDP), 800 μg daily, during the third year. The FEV1 and provoking concentration of histamine producing a 20% fall in FEV1 (PC20-histamine) were assessed at six-monthly intervals.

In asthma, the annual decline in prebronchodilator FEV1 of -158 ml·yr⁻¹ during bronchodilator therapy alone was followed by a significant increase of 562 ml·yr⁻¹ during months 1–6 of BDP treatment (p<0.0005). During months 7–12 of BDP, the FEV1 declined slightly with -31 ml·yr⁻¹, which was not statistically different from the annual decline before steroid therapy (p=0.17). In COPD, the increase of 323 ml·yr⁻¹ during months 1–6 of treatment with BDP was different from the annual decline of -158 ml·yr⁻¹ before BDP (p<0.05). The PC20-histamine improved by 3.8 doubling doses during 1–12 months of BDP in asthma (p<0.05) but not in COPD. The weekly measured peak expiratory flow rate (PEFR) improved by 16.7% from the start of BDP therapy in asthma (p<0.0009) and by 4.5% in COPD (p<0.05). In comparison with bronchodilator therapy alone, the number of exacerbations decreased by 0.7·yr⁻¹ in asthma (p<0.0001) but not in COPD. In both asthma and COPD, the diurnal variation of the PEFR and the severity of weekly recorded symptoms diminished during BDP treatment (p<0.05).

It was concluded that inhaled BDP, 800 μg daily, improved the course of asthma and COPD in comparison with bronchodilator therapy alone. The effects of BDP in asthma were more pronounced than in COPD.

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Both asthma and chronic obstructive pulmonary disease (COPD) are more or less progressive diseases at an adult age [1–4]. The decline in ventilatory function is, on average, two to four times higher in patients [1, 2] than in random samples of the population [5, 6]. At an advanced stage of the disease, severe limitations in activities of daily life may occur as a consequence of a low ventilatory capacity [7]. Patients with a rapid deterioration of pulmonary function are probably at risk of early disability or death from chronic airway obstruction [8]. Some retrospective, uncontrolled studies have suggested that corticosteroids might slow down the progression of chronic airway obstruction [9]. Unfortunately, this suggestion has never been tested in long-term, prospective, controlled studies. Whether inhaled steroids could improve the course of asthma and COPD in comparison with bronchodilator therapy alone was investigated in the present prospective, controlled study. At an earlier stage, the patients in this study (28 asthma, 28 COPD) participated in a randomized, controlled, intervention study with bronchodilators [10–12]. During two years of treatment with only one bronchodilator (salbutamol or ipratropium bromide), patients had demonstrated an average decline in forced expiratory volume in one second (FEV1) of 160 ml·yr⁻¹ in combination with almost 2
exacerbations-yr⁻¹. Therefore, in the third year, they were additionally treated with inhaled beclomethasone dipropionate (BDP), 800 µg daily. In this study, the hypothesis that inhaled BDP is able to decelerate the annual decline in FEV₁, in comparison with bronchodilator therapy alone was tested.

Methods

Patients

The patient selection in the preceding bronchodilator intervention study was described in detail previously [10–12]. Briefly: 29 general practitioners in the catchment area of Nijmegen University were asked to select all patients of ≥30 yrs with symptoms of asthma and COPD. Only those patients who showed mild to moderate airway obstruction (FEV₁ < FEV₁ % predicted [13] minus 2 standard deviations, but >50% predicted) and/or bronchial hyperresponsiveness to histamine (provoking concentration of histamine producing a 20% fall in FEV₁, (PC₂₀) ≤ 8 mg·ml⁻¹) were included by the investigators. Patients, dependent on inhaled corticosteroids, with chronic heart failure, malignant disorders, or other severe life-threatening diseases, were excluded. One hundred and sixty patients completed the bronchodilator trial. During the two years of bronchodilator treatment, a rapid decline in FEV₁ (≥80 ml-yr⁻¹) and a relatively high exacerbation rate (≥2-yr⁻¹) was observed in a subgroup of 56 patients (35%). These patients were selected for additional treatment with inhaled BDP in the third year. The detailed selection criteria are shown in Table 1.

Table 1. – Selection criteria of the patients with fast progressive disease, treated with BDP during the third year of study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Age yrs</td>
<td>49(12)</td>
<td>54(12)</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>12/16</td>
<td>16/12</td>
</tr>
<tr>
<td>Pack years</td>
<td>13(14)</td>
<td>* 23(3))</td>
</tr>
<tr>
<td>Smokers +/-</td>
<td>14/14</td>
<td>17/9</td>
</tr>
<tr>
<td>Cigarettes-day⁻¹</td>
<td>3.4(5.3)</td>
<td>** 8.9(8.5)</td>
</tr>
<tr>
<td>Allergy +/- #</td>
<td>14/14</td>
<td>*** 2/24</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>67(17)</td>
<td>70(16)</td>
</tr>
<tr>
<td>FEV₁/JVC %</td>
<td>57(15)</td>
<td>63(13)</td>
</tr>
<tr>
<td>BDR-FEV₁ %</td>
<td>14(9)</td>
<td>* 7(4)</td>
</tr>
<tr>
<td>Di-PEFR %</td>
<td>12.4(8.0)</td>
<td>23(3)</td>
</tr>
<tr>
<td>PC₂₀ mg·ml⁻¹</td>
<td>0.8</td>
<td>*** 6.2</td>
</tr>
</tbody>
</table>

#: allergy was defined as one positive test out of seven RAST. * p<0.05; ** p<0.01; *** p<0.001; t p=0.055. Differences between asthma and COPD were statistically compared with the unpaired Student's t-test for normally distributed variables and with the Chi-squared test for dichotomic variables. Standard deviation in parentheses. BDR-FEV₁: increase in forced expiratory volume in one second after bronchodilation with 80 µg ipratropium bromide and 400 µg salbutamol; Di-PEFR: diurnal peak expiratory flow rate index; COPD: chronic obstructive pulmonary disease; FEV₁/JVC: FEV₁, as a percentage of inspiratory vital capacity; PC₂₀, provoking concentration of histamine causing a 20% fall in FEV₁; RAST: radio-allergosorbent test.

Study design and treatment

At the start of the three year intervention study, the patients were randomly allocated to one of the two parallel treatment regimens: continuous or on-demand therapy with a bronchodilator. The patients used salbutamol during one year and ipratropium bromide during the other year. The sequence of the drugs was determined by random allocation [10]. During the third year, the 56 patients were additionally treated with 800 µg BDP daily in combination with 1,600 µg salbutamol or 160 µg ipratropium bromide daily (all dry powder inhalations). The bronchodilator inhaled during the second year was also used in the third year. Once every three months, proper inhalation of the medication
oral prednisone was given.

During the first two years of study, 27 of the 56 patients received bronchodilator therapy on-demand (15 asthma, 12 COPD). The mean daily number of inhalations of salbutamol (400 μg per inhalation) or of ipratropium bromide (40 μg per inhalation) in the patients treated on-demand was 1.2 (SEM 0.3) in asthma, 0.8 (0.2) in COPD. During the third year, 28 patients used salbutamol (15 asthma, 13 COPD), 28 ipratropium bromide (13 asthma, 15 COPD). During the third year, all patients used bronchodilators continuously; during the first and second year, only those patients in the continuous treatment group.

**Pulmonary function, nonspecific bronchial responsiveness**

The FEV₁, bronchial responsiveness to histamine (PC₂₀-histamine values) and reversibility of airway obstruction were assessed at six monthly intervals. All measurements were carried out by two qualified laboratory assistants by means of the Microspiro HI-298® (Chest Corp., Japan) [14]. No bronchodilator was inhaled during at least 8 h prior to the ventilatory function tests. Firstly, dynamic spirometry was performed. The best of three forced expiratory manoeuvres, with the highest sum of the forced vital capacity (FVC) and FEV₁, was used for data analysis. Secondly, bronchial responsiveness to histamine was measured according to the method described by Cockcroft et al. [15]. Results were expressed as the provocative concentration of histamine required to produce a 20% fall in FEV₁ (PC₂₀). After the FEV₁ had returned to the baseline value, the bronchodilator responsiveness was assessed 60 min after the administration of 80 μg ipratropium bromide and 400 μg salbutamol (metered dose aerosol). The bronchodilator responsiveness was expressed as the relative increase of FEV₁, compared to the predicted value of the FEV₁.

**Peakflow assessments**

Peak flow measurements were performed with the Assess peak flow meter in the morning and in the evening, weekly on the same day and time [16]. The highest value of three measurements was taken for analysis. The diurnal peak expiratory flow rate (PEFR) index (absolute difference between evening value and morning value divided by the highest value) was calculated.

**Exacerbations**

Exacerbations were defined according to Fletcher et al. [1] with the small modifications of Boman et al. [17]. In case of an exacerbation, a 10 day course with oral prednisone was given.

**Symptoms and adverse effects**

All patients made weekly recordings of the presence and severity of symptoms (cough, phlegm, dyspnoea) on a scale of 0–4. Adverse effects of medication (dysphonia and oropharyngeal irritation) were recorded by the patients once every three months. In addition, every six months, the presence and severity of oral candidiasis was assessed by means of a questionnaire.

**Smoking habits**

At the start of the study, the smoking history was assessed retrospectively in pack years. During the study, the average number of cigarettes smoked per day was also recorded in the diary on a weekly basis.

**Analysis**

Values of outcome variables before the use of BDP were compared with data during steroid treatment. Differences were tested with Student's paired t-test for normally distributed variables and the Chi-squared test for dichotomic variables. Prior to analysis, the PC₂₀ values were log transformed. The annual change in FEV₁ and PC₂₀ was calculated by linear regression of FEV₁ and logPC₂₀ in the course of time. A possible influence of the preceding bronchodilator treatment (continuous versus on-demand) or of the bronchodilator in the third year (salbutamol versus ipratropium bromide) on the changes in outcome variables during steroid treatment was assessed by multiple analysis of variance (MANOVA).

**Results**

Forty-eight of the 56 patients completed one year of treatment with BDP. Reasons for drop-out were: refusal to inhale steroids (one asthma, one COPD), bronchial carcinoma (one COPD), chronic heart failure (one COPD), persistent oral candidiasis and dysphonia (one COPD), serious non-compliance (one COPD) and personal reasons (one asthma, one COPD).

**Asthma**

In asthma, the pre- and postbronchodilator FEV₁ increased by 0.28 (SEM 0.07) l and 0.10 (0.05) l, respectively, during months 1–6 of steroid treatment (p=0.0009 and p=0.070, respectively) (fig. 1). These increases in ml·yr⁻¹ were significantly different from the annual declines measured before steroid treatment (table 3). During months 7–12 of BDP treatment, the prebronchodilator FEV₁ deteriorated slightly by -31 ml·yr⁻¹ but tended to remain different from the annual decline of -158 ml·yr⁻¹ before steroid treatment (p=0.170) (table 3).
A) Asthma

B) COPD

Fig. 1. - The course of the prebronchodilator (---) and postbronchodilator (•--•) FEV₁ during the three years of study. The standard errors of the mean are also represented. Differences in FEV₁ after six and 12 months of treatment with BDP were compared with the initial values at the start of the BDP period (month 24 in the figure) by means of the Student's paired t-test. FEV₁: forced expiratory volume in one second; BDP: beclomethasone dipropionate. A) Asthma: *: p<0.001; +: p=0.070; †: p=0.321. B) Chronic obstructive pulmonary disease (COPD): †: p=0.092; ‡: p=0.288.

Table 3. - The outcome variables in the period before, during months 1–6 and months 7–12 of treatment with BDP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment with BDP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>Change FEV₁-pre ml·yr⁻¹</td>
<td>-158(26)</td>
</tr>
<tr>
<td>Change FEV₁-post ml·yr⁻¹</td>
<td>-115(23)</td>
</tr>
<tr>
<td>Change PC₂₀ doubling dose-yr⁻¹</td>
<td>-0.38(0.80)</td>
</tr>
<tr>
<td>Diurnal PEFR index %</td>
<td>13.2(1.6)</td>
</tr>
<tr>
<td>Exacerbations n·yr⁻¹</td>
<td>13.3(2.2)</td>
</tr>
<tr>
<td>Total symptom score</td>
<td>3.9(0.8)</td>
</tr>
<tr>
<td>Cough score</td>
<td>0.74(0.15)</td>
</tr>
<tr>
<td>Phlegm score</td>
<td>0.71(0.12)</td>
</tr>
<tr>
<td>Dyspnoea score</td>
<td>0.99(0.17)</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
</tr>
<tr>
<td>Change FEV₁-pre ml·yr⁻¹</td>
<td>-156(26)</td>
</tr>
<tr>
<td>Change FEV₁-post ml·yr⁻¹</td>
<td>-77(23)</td>
</tr>
<tr>
<td>Change PC₂₀ doubling dose-yr⁻¹</td>
<td>-0.51(0.46)</td>
</tr>
<tr>
<td>Diurnal PEFR index %</td>
<td>10.8(1.4)</td>
</tr>
<tr>
<td>Exacerbations n·yr⁻¹</td>
<td>1.8(0.3)</td>
</tr>
<tr>
<td>Total symptom score</td>
<td>6.2(0.7)</td>
</tr>
<tr>
<td>Cough score</td>
<td>1.1(0.17)</td>
</tr>
<tr>
<td>Phlegm score</td>
<td>1.0(0.10)</td>
</tr>
<tr>
<td>Dyspnoea score</td>
<td>1.5(0.16)</td>
</tr>
</tbody>
</table>

†: p<0.10; *: p<0.05; **: p<0.005; ***: p<0.0005; ****: p<0.0001. The values during BDP therapy were compared with the values before BDP treatment by Student's paired t-test. Data are presented as mean and SEM in parentheses. For exacerbations, the value in the whole year of BDP is shown. PEFR: peak expiratory flow rate. FEV₁-pre: prebronchodilator FEV₁; FEV₁-post: postbronchodilatation FEV₁. For further abbreviations see legends to table 1 and 2.
Fig. 2. - The course of the PC<sub>20</sub> during the three years of study. The standard errors of the mean are also represented. Differences in PC<sub>20</sub> after six and 12 months of treatment with BDP were compared with the initial value at the start of the BDP period (month 24 in the figure) by means of the Student's paired t-test. PC<sub>20</sub>: provoking concentration of histamine producing a 20% fall in forced expiratory volume in one second; BDP: beclomethasone dipropionate. A) Asthma: +: p=0.252; *: p=<0.05. B) Chronic obstructive pulmonary disease (COPD): +: p=0.124; †: p=0.066.

Fig. 3. - The course of the peakflow during three years. The peakflow during treatment with BDP was statistically compared with the value just before the start of BDP treatment by means of the Student's paired t-test. The standard errors are also represented. PEFR: peak expiratory flow rate; BDP: beclomethasone dipropionate. A) Asthma: *: p=0.01; **: p=0.001. B) Chronic obstructive pulmonary disease (COPD): +: p=0.274; †: p=0.055; ‡: p=0.533.
During BDP treatment, the peakflow increased by 16.7(5.7)% and the PC_{20} improved by 3.8(1.4) doubling doses from the value at the start of treatment with BDP (p=0.0009 and p=0.024, respectively) (figs 2 and 3). The number of exacerbations per year, the severity of symptoms (cough, phlegm and dyspnoea) and the diurnal variation of the peakflow decreased during treatment with BDP (table 3).

**COPD**

In COPD, the effects of 800 µg BDP daily were less apparent than in asthma. Although the prebronchodilator FEV₁ increased by 0.16 (SEM 0.09) l in the first six months of treatment with BDP (this increase was different from the annual decline before the use of BDP, p=0.041), during months 7–12 the FEV₁ decreased by -141 ml·yr⁻¹ (table 3 and fig. 1). During the year's treatment with the steroid, the peakflow increased by 4.5(2.3)% whereas the PC_{20} tended to decrease by 1.8(0.9) doubling dose (p=0.055 and p=0.066, respectively) (fig. 2 and 3). The average number of exacerbations per year was not influenced by BDP (table 3). The severity of symptoms decreased during months 7–12 of treatment (table 3). Moreover, BDP diminished the diurnal variation of the peakflow (table 3).

**Adverse effects**

During one year's treatment with steroids, 14% of patients developed oral candidiasis (Chi-squared test, p=0.007). Moreover, complaints of dysphonia tended to increase during steroid treatment (Chi-squared test, p=0.095).

**Influence of bronchodilator therapy preceding and during steroid treatment**

No influence of the treatment regimen in the first two years (continuous or on-demand), or of the type of bronchodilator (salbutamol or ipratropium bromide) in the third year, could be demonstrated on the changes in outcome variables during steroid treatment.

**Smoking during the study**

In asthma, the proportion of current smokers/nonsmokers was 14/14 during the first two years, 11/17 during the third year (p>0.05, two-samples, paired proportion test). Two of the three asthmatics who stopped smoking during the third year had smoked <0.1 cigarettes·day⁻¹ during bronchodilator treatment alone. Therefore, these patients were almost nonsmokers during the 3 yr intervention study. In COPD, the proportion of current smokers/nonsmokers was 19/9 during the first two years, 18/10 during the third year (p>0.05, two-samples, paired proportion test). One patient with COPD stopped smoking during the third year. However, this patient was not incorporated in our analysis because of serious non-compliance to BDP.

**Discussion**

This study confirmed the hypothesis that daily inhalation of BDP, 800 µg, during one year can decelerate the decline in FEV₁, during bronchodilator treatment alone in both asthma and COPD. In asthma, steroid treatment during one year even reversed the deterioration during two year bronchodilator treatment. However, this effect was less apparent in patients with COPD.

**Study design**

In this self-controlled study, values of outcome measurements during bronchodilator therapy alone were compared with those during additional inhaled cortisoloid therapy (within-patient comparison of treatments). This design can produce results that are statistically and clinically valid when no period ("natural variation") or carry-over effects (influence of preceding medication) are present [18]. Our study meets these criteria for a valid self-controlled design. Therefore, from a methodological point of view, a placebo group was not absolutely necessary in this trial and, more importantly, from an ethical point of view even unacceptable. It is unethical to treat patients with an annual decline in FEV₁ of -160 ml·yr⁻¹ and almost two exacerbations per year with a placebo. In our study, no carry-over effect of the preceding bronchodilator medication in either of the outcome variables during steroid treatment could be demonstrated. No period effect was assessed in the number of exacerbations. Neither in COPD patients who were treated with BDP, nor in those COPD patients from the inter-vention study (treated with bronchodilators alone during the third year of study) did a change in exacerbations occur. A period effect in FEV₁ decline is not probable. The within-patient decline was assessed by linear regression of seven measurements of the FEV₁ during two years with a relatively high percentage of explained variance (31%). Moreover, regression-to-the-mean (because of our selection of patients with a decline in FEV₁ of >80 ml·yr⁻¹ during bronchodilator therapy alone) did not explain the observed changes in FEV₁ during BDP therapy. We calculated the effect of regression-to-the-mean in annual decline of FEV₁, by means of the equations presented by Gardner and Head [19] and Das and Mulder [20]. This effect appeared to be 28(SEM 7) ml·yr⁻¹ in asthma and 28(12) ml·yr⁻¹ in COPD. After adjusting the changes in FEV₁ during BDP therapy for regression-to-the-mean, almost the same results were found (the unadjusted versus adjusted changes in prebronchodilator FEV₁ during 0–6
months of BDP were $+562$ and $+547$ ml-yr$^{-1}$ in asthma, $+323$ and $+309$ ml-yr$^{-1}$ in COPD, respectively). The adjusted changes remained statistically different from the decline before steroid therapy in both asthma and COPD. Therefore, the observed changes in outcome measurements were a real reflection of the effects of inhaled BDP treatment.

Effects of corticosteroids

In asthma, the course of the FEV$_1$, the peakflow and the PC$_20$ improved during BDP treatment in comparison with bronchodilator therapy alone. BDP was also useful in the prevention of exacerbations, the reduction of respiratory symptoms and diminution of the diurnal variation of the peakflow. BDP not only decelerated the annual decline of the FEV$_1$ in asthma but almost completely reversed the deterioration in pulmonary function and bronchial hyperresponsiveness during the preceding two years. In COPD, the effects of BDP were less apparent. Although an improvement in FEV$_1$, and peakflow was observed, the PC$_20$ and the number of exacerbations were not influenced by BDP. The steroid did reduce the severity of symptoms and the diurnal variation of the peakflow.

Corticosteroids probably act on various components of the inflammatory response [21, 22]. They inhibit the release of mediators from macrophages and eosinophils [21], microvascular leakage and influx of inflammatory cells in the lungs. Late and (after prolonged treatment) early responses to allergens are blocked by steroids [22]. Several studies in asthma have demonstrated beneficial effects of inhaled steroids on the ventilatory function, bronchial hyperresponsiveness and respiratory symptoms [23-27]. The efficacy of corticosteroids in the treatment of COPD is less clear than in asthma [28]. This prospective controlled study is the first long-term one showing that an inhaled steroid (BDP), of 800 µg daily, during one year has several beneficial effects in patients with COPD. A relatively large increase in FEV$_1$ was found during the first six months of BDP treatment in COPD. This was followed by a slight (statistically nonsignificant) fall during the subsequent 6 months of BDP treatment. Longer follow-up is necessary to evaluate whether this trend proceeds or not. The treatment with BDP in all patients was continued for another year. The differences in efficacy of BDP between asthma and COPD were not caused by a better compliance to BDP in asthma than in COPD. A study of the patient compliance to BDP by counting capsules (single-blind) revealed that no difference between asthma and COPD existed in this respect [29]. Patients had used on average 86% of the prescribed dose of BDP.

Adverse effects of inhaled steroids

No serious adverse effects are recorded from inhaled corticosteroids [30]. With a daily dose <1,500 µg, no inhibition of the hypophyseal-pituitary-adrenal axis or other systemic effects were observed [21]. In fact, dysphonia and oral candidiasis are the most serious side-effects [31]. In our study, 14% of the patients suffered from oral candidiasis. When the BDP was inhaled through a spacer device [31], the complaints diminished or disappeared and the patients (with the exception of one) were able to continue steroid treatment.

Bronchodilator versus anti-inflammatory therapy

In several recent reviews, inhaled corticosteroids have been advocated as a first line therapy in asthma, which should be introduced at an early stage [21, 32]. Bronchodilators may not influence inflammation, may mask the inflammatory processes by relieving symptoms and may increase the exposure to allergens, cigarette smoke and other irritants [10, 11, 21]. The findings of our previous study showed that regular versus on-demand use of a bronchodilator (salbutamol or ipratropium bromide) without anti-inflammatory medication was accompanied by an accelerated annual decline in ventilatory function in both asthma and COPD [10]. These results corresponded to the findings of Sarks et al. [33]. The most important observation of the present study was that in asthma deleterious effects of bronchodilator therapy alone during two years were almost completely abolished by additional treatment with BDP during one year. However, in COPD, the adverse effects were only partly reversible. Although the two year deterioration of the ventilatory function and bronchial hyperresponsiveness was reversible in asthma, it is advisable to start with inhaled steroids at an early stage of the disease, particularly when the pulmonary function deteriorates rapidly. Chronic inflammation may lead to irreversible changes [3] such as hypertrophy of airway smooth muscle and thickening of basement membrane, which are probably inhibited by early steroid therapy [21].

It was concluded that inhalation of BDP, 800 µg daily, during one year improved the long-term course of asthma and COPD in comparison with bronchodilator therapy alone. The effects of BDP were larger in asthma than in COPD.

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