High-dose beclomethasone: oral steroid-sparing effect in severe asthmatic patients


ABSTRACT: One hundred and twenty four patients with severe asthma requiring maintenance treatment with oral corticosteroids were included in a multicentre, double-blind, randomized study comparing the effects of inhaled beclomethasone dipropionate (BDP) (250 µg/puff), beginning with 1,000 µg daily, vs placebo (P). Pulmonary function was assessed and dosage of prednisone and BDP (or P) were adjusted every 15 days according to a clinical score.

Our results showed, after 3 months: 1) A greater drop-out rate in the P group than in the BDP group (36 vs 6%, respectively, p<0.01); 2) A total weaning from prednisone in 76% of patients in the BDP group (mean BDP dosage = 1.270±340 µg/day, mean±sd), vs 34% in the P group (p<0.001). The mean daily dosage of prednisone was reduced from 17±7.5 mg to 3.1±7.4 mg in the BDP group vs 15.6±7.7 mg to 9.1±9.4 mg in the P group (p<0.001) without any relationship between the steroid-sparing effect and the initial dosage of prednisone; 3) Mean change in forced expiratory volume in one second (FEV1) was +7±21% from the initial value in the BDP group vs -6±20% in the P group; p<0.01.

Thus, in patients with severe asthma requiring oral corticosteroids, high-dose BDP has an important oral steroid-sparing effect not related to the initial dosage of oral steroids and allows a better control of airway obstruction than oral corticosteroids alone.


The efficacy and dose-dependency of inhaled beclomethasone dipropionate (BDP) in controlling the symptoms and bronchial obstruction of chronic asthma and the dose-response relationship have already been demonstrated [1–3].

To our knowledge no placebo-controlled prospective study has been published evaluating the oral corticosteroid-sparing effects of high-dose BDP treatment with a conventional pressurized metered-dose inhaler (MDI) delivering 250 µg per puff.

The purpose of this study was to compare the effects of treatment with high-dose BDP to those of similar treatment with placebo (P) on: 1) the requirement for oral corticosteroids in patients with chronic asthma requiring maintenance treatment with oral corticosteroids; 2) the control of asthma.

Patients and methods

The trial was performed in 12 co-operating centres, studying each patient over three months after obtaining oral informed consent. One hundred and twenty four patients (58 males and 66 females) suffering from chronic asthma, age 52.2±11.5 yrs (mean±sd) were enrolled. The number of patients per centre ranged from 7–12.

All patients suffered from asthma meeting American Thoracic Society (ATS) criteria [4]. On inclusion, all patients responded with a significant increase in forced expiratory volume in one second (FEV1) to 200 µg inhaled salbutamol. They had chronic asthma since the disease had been diagnosed more than 10 yrs earlier for most of them. Severity was assessed from the requirement for daily maintenance treatment with corticosteroids. For inclusion, patients had to be treated with 5 mg or more per day of oral prednisone (or prednisolone), with a minimum of 5 mg for at least 60 days over the three preceding months. Most had been treated with oral glucocorticosteroids for more than one year. The mean daily doses of oral corticosteroid taken by the patients in the two groups at entry into the study were also similar (17.1±7.5 mg in the BDP group; 15.6±7.7 mg in the P group; p>0.1). Distribution of the patients according to the dosage of oral corticosteroids received at the time of inclusion in the study is indicated in figure 1.

Exclusion criteria comprised: patients under 15 yrs; who had received long-acting or inhaled corticosteroid treatment during the two preceding months; unable to
use correctly and regularly a metered dose inhaler (MDI); having chronic obstructive pulmonary disease (COPD) particularly those who smoked more than 20 cigarettes a day; or having respiratory tract infection particularly tuberculosis.

At each visit a clinical score was established on the basis of the presence of each one of the following criteria (each of them scored 1) recorded in the personal diary: 1) Occurrence of asthmatic crisis defined as an increase of usual symptoms noted by the patient: wheezing, breathlessness, chest tightness, cough and/or hypersecretion. These symptoms should require treatment by $\beta_2$-agonists but not by corticosteroids. 2) Occurrence of dyspnoea on a graded exertion, also requiring inhalation of $\beta_2$-agonists. 3) Decrease of at least 15% in mean peak expiratory flow rate (PEF) values during the five days before the visit. Thus, the clinical score ranged from 0–3 and was used as a basis for adjusting the treatment as described below.

The dosage of oral prednisone and/or the number of inhalations from the MDI (BDP or P) was fixed at each visit according to the clinical score as follows: 1) Clinical score = 0 or 1, suggesting good control: the daily dosage of prednisone was reduced by 5 mg without changing the inhaler use. 2) Clinical score = 2 or 3, suggesting bad control: daily dosage of inhaler was increased by 2 puffs (i.e. from 4 to 6 puffs or from 6 to 8 puffs) without changing the dose of prednisone. If 8 puffs per day were already being taken, the dosage of prednisone was increased by 5 mg without changing the number of puffs·day$^{-1}$ until the end of the study.

Throughout the study, all other maintenance medications used for the treatment of asthma were kept unchanged for each patient. Any additional medication used was noted in the personal diary.

If lack of control occurred with a need for treatment by oral corticosteroids, patients were treated, regardless of the dose of oral corticosteroids, by a seven day course of oral prednisone or prednisolone at 0.5 mg·kg$^{-1}$·day$^{-1}$, afterwards returning to the previous dosage. We defined a favourable response as 50% reduction in oral corticosteroid requirements. We calculated that a total of 128 patients would be needed to show a difference of 30% between the two groups assuming a response state of 30% in the P group, with a 0.05 type I error and a 0.05 type II error, using a one-sided test. Response to treatment was assessed on D84. If treatment was interrupted for any reason the response was considered as failure in the analysis.

Comparisons of the two groups were performed by means of the Fisher exact test, one-way analysis of variance and a correlation test as appropriate. An analysis of factors predicting treatment response made use of multiple logistic regression involving continuous variables (age, gender, duration of asthma, smoking habits, pulmonary function tests). A stepwise procedure was used.

**Results**

The two groups of patients (BDP: n=63; P: n=61) were similar in all respects (age, medication use, FEV$_1$, smoking history) at the beginning of the study, except for the distribution of gender (table 1).
Patients' percentage sparing was not statistically correlated in either group to the initial dosage being taking at D0. The relationship between the percentage sparing and the initial dosage of oral corticosteroids was not significant in either group.

These results lead to a type I error, one-sided test.

Mean dosage of oral corticosteroid at D84 was 15±7 mg in the BDP group versus 59±25 mg (p<0.001). The number of patients remaining under study is given in parenthesis. The data are presented as means±deviations. PEF: peak expiratory flow; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; BDP: beclomethasone dipropionate; P: placebo.

Four patients stopped their treatment soon after starting and were not seen at D14. All of them belonged to the placebo group. Twenty-two other patients stopped their treatment at various times before the end of the study. Thus, 26 patients interrupted their treatment and were counted as failures. Of these, 22 out of 61 (36%) were in the P group (relapse of asthma 10; inefficacy 5; nasal obstruction 1; others 6) and 4 out of 63 (6%) were in the BDP group (inefficacy 2; others 2) (p<0.001).

A total oral corticosteroid-sparing effect (defined as the number of patients that were able to discontinue oral corticosteroid treatment) was obtained at D84 for 69 patients, 48 patients (76%) in the BDP group and 21 patients (34%) in the P group (p<0.001).

Figure 2 shows the change with the time in the proportion of patients for whom oral corticosteroids were decreased by at least 50%. These proportions were 86% at D42 and 90% at D84 in the BDP group versus 59% and 48% respectively in the P group (p<0.001 at D84). These results lead to a type II error of less than 1% with 0.05 type I error, one-sided test.

These data relate to all patients included in the trial, taking into account patients who dropped out and for whom the dosage of oral corticosteroids did not change. The mean dosage of oral corticosteroid at D84 was 3.1±7.4 mg in the BDP group versus 9.1±9.4 mg in the P group. These dosages represent an 84% decrease in dose in the BDP group versus 43% in the P group (p<0.001).

Our analysis showed that the final dosage of oral corticosteroids was not statistically correlated in either group to the initial dosage being taking at D0. The relationship between the percentage sparing and the initial dosage of oral corticosteroid was not significant in either group.

However, most patients (95%) in the BDP group with an initial dosage or oral corticosteroids lower than 15 mg·day⁻¹ (class A) were completely weaned off oral corticosteroids, compared with 44% in the P group. For higher initial dosages (class B: 15–25 mg·day⁻¹ and class C: >25 mg·day⁻¹) a similar proportion of patients in the BDP group could be weaned (69 and 63%, respectively), whereas in the P group only 32% of the class B patients and none of the class C could be weaned off oral corticosteroids.

The mean daily dose of BDP required to obtain total sparing was 1,270±340 μg·day⁻¹. Twenty seven patients received four puffs of BDP (1,000 μg), 16 patients six puffs (1,500 μg) and only 5 patients needed eight puffs (2,000 μg) to be weaned off oral prednisone.

The mean change in baseline FEV1 from the initial value at D0 to that at D84 was positive (+7±21%) in the BDP group and negative (-6±20%) in the P group (fig. 3); this difference between the groups was significant (p<0.01), as was the difference in the change in FVC (p<0.05). Change in FEV1, obtained after salbutamol (200 μg by MDI) from the initial value at D0 to that at D84 was also positive (+14±45%) in the BDP group and negative (-4±27%) in the P group (p<0.05); the difference in the change in FVC caused by salbutamol in the two groups was not significant at D84. As shown in figure 3, the mean change in FEV1, in the BDP group was maximum as early as D14, and it decreased slightly but significantly during the trial. Similar to the changes in baseline FEV1, the mean FEV1 after salbutamol in the BDP group was maximum at D14 and did not change significantly during the study.

PEF on D84 was significantly higher in the BDP group (n=56) than in the P group (n=40): 53±16% of the predicted value versus 45±15% (p<0.05). A good correlation between FEV1 and PEF was noticed throughout the study in both groups (r=0.63 to 0.73; p<0.01 from D14 to D84).

Table 1. Patients' characteristics on inclusion

<table>
<thead>
<tr>
<th></th>
<th>BDP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td>Male</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>39</td>
</tr>
<tr>
<td>Age yr</td>
<td>53±10</td>
<td>51±13</td>
</tr>
<tr>
<td>Age at onset of asthma yr</td>
<td>15±2</td>
<td>13±2</td>
</tr>
<tr>
<td>Current smokers %</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Permanent respiratory discomfort %</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>PEF % pred</td>
<td>43±15</td>
<td>47±16</td>
</tr>
<tr>
<td>FEV1 % pred</td>
<td>58±25</td>
<td>63±22</td>
</tr>
<tr>
<td>FVC % pred</td>
<td>80±24</td>
<td>85±25</td>
</tr>
<tr>
<td>Visual analogue scale (VAS)</td>
<td>59±26</td>
<td>58±25</td>
</tr>
</tbody>
</table>

(100 mm line diagram)

Other medications used %

- Beta₂-agonist
- Anticholinergics
- Aminophylline

Daily dose of oral prednisone or prednisolone on inclusion mg

BDP: 17±7.5; P: 15.6±7.7

Data are presented as means±standard deviation. PEF: peak expiratory flow; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; BDP: beclomethasone dipropionate; P: placebo.
Scores on the VAS were higher in the BDP group than in the P group throughout the study (p<0.01 from D14 to D84) (fig. 4). Mean clinical scores on D84 were 0.4±0.9 in the BDP group and 1.1±1.2 in the P group (p<0.01).

Asthma attacks requiring a short course of higher doses of oral corticosteroids were more frequent in the P group (38%) than in the BDP group (22%) (p=0.06). These patients were kept in the statistical analysis for the evaluation of the response to treatment.

In both groups the treatments were well-tolerated. Side-effects were observed in ten patients, six (10%) in the BDP group and four (7%) in the P group. In all of these cases the side-effects were minor (hoarseness, oral candidiasis, sore throat) and did not require that treatment be stopped, except in one patient in the P group who complained of severe nasal obstruction. Improvement of adrenal function tests after substitution of inhaled for oral corticosteroids was not evaluated.

The search for predictive factors of response to high dose BDP treatment was carried out by a multiple logistic regression. If total sparing was considered as success, the three variables with a specific prognostic value were the treatment (BDP or P) (p<0.001), a low initial FVC (p<0.001) and, to a lesser extent, youth (p=0.03). Concerning the oral treatment, it appeared that the reduction of prednisone between DO and D84 was similar irrespective of the initial dose of oral corticosteroid.

**Discussion**

Inhaled corticosteroids have been used in the treatment of chronic asthma for the past ten years and their efficacy has been demonstrated in a number of studies, especially when high doses are used [5–7].

The first demonstration of a dose-response relationship between the effects of BDP and symptoms or bronchial obstruction was established by Tooood et al. [3] in patients poorly controlled by oral corticosteroids. With the MDI delivering 250 μg BDP-puff, Costello and Clark [8] showed, in five patients an increase in pulmonary function as the daily dose of BDP increased from 400 μg to 1,000 μg.

In a retrospective study of 293 asthmatic patients poorly controlled by 400–800 μg·day⁻¹ of BDP in addition to oral corticosteroids, Smith and Hodson [9] showed a total sparing of oral steroids with high-dose BDP up to 2,000 μg·day⁻¹, with better control of asthma. These studies and others (5–7, 10) suggest not only a good sparing effect on oral steroids, but also better control of the disease by high-dose inhaled steroids.

In our study, 90% of patients in the BDP group had their oral steroid treatment reduced to less than half of their initial dose, and 76% of patients were weaned from oral corticosteroids altogether. This weaning from oral prednisone was obtained with a mean daily dose of BDP of 1,270 μg, but more than half of the patients needed only 1,000 μg (27 out of 48). Therefore, the oral steroid-sparing effect of BDP was of major importance. It must be noted, however, that a sparing effect was noticeable even with placebo inhalation, since 34% of patients treated with P were totally weaned off oral corticosteroids. Another explanation could contribute to this finding: during the preparatory period, no attempt to reduce the dosage of oral steroids was made, so that our study design may have exaggerated this effect. Examination of the time-dependent changes in the proportion of patients able to decrease the dose of oral steroids by at least 50% is very instructive: this proportion is almost at the maximum from the sixth week in the patients treated with BDP and remains stable thereafter. In marked contrast, this proportion is also at
the maximum in the P group after six weeks but falls
some weeks later, due to a recurrence of symptoms in
many patients in the group. It appears that the placebo
effect is not as effective after six weeks as at the begin-
n ing. This oral steroid-sparing effect of high doses of
inhaled BDP was not unexpected. However, our obser-
vation is important, since it shows that oral
corticosteroids can be reduced or even stopped in many
asthmatic patients treated with placebo aerosol therapy,
a finding that cannot be demonstrated in retrospective
studies.

The second conclusion to be drawn from our results
is the effect of BDP on bronchial obstruction, assessed
by pulmonary function, and on symptoms of asthma:
inhaled BDP caused a better control of asthma than did
oral corticosteroids alone. These findings are of major
importance. From D0 to D14 mean FEV$^1$, increased from
the initial values by 11±19% in the BDP group whereas
the change in the P group was only ±14% over the
same period. This effect was persistent since at the end
of the study (D84) mean FEV$^1$, was still increased by
7±21% in patients treated by BDP and had decreased by
6±20% in the placebo group (fig. 3). The other pa-
rameters enabling the assessment of the control of asthma
(dyspnoea assessed by VAS or bronchial obstruction
assessed by PEF) also showed that a significant dif-
ference between the groups rapidly occurred and persisted
throughout the three-month study.

An indirect parameter to assess an improvement in
control is the drop-out ratio. This was much higher in
P group than in the BDP group: 15 out of 61 patients
stopped their treatment because of recurrence of asthma
symptoms or inefficacy in the P group compared with
2 out of 63 in the BDP group. Thus, an additional
treatment with inhalations of high-dose beclomethasone
in asthmatic patients treated with oral corticosteroids
can result in better control of asthma as soon as two
weeks after the beginning of the treatment, and this
effect persists for at least three months. Two possible
hypotheses may explain this effect: firstly, inhaled
steroids deposited directly on bronchial mucosa may
increase the concentration of steroid molecules within
the tissue and, thus, may act more efficiently than oral
steroids alone. We are not aware of any studies compar-
ing steroid concentrations in bronchi after inhalation
and after oral intake. This could be of great interest.
Secondly, it is possible that a different steroid molecule
such as BDP can bind to specific receptors in a better
way than prednisone alone and, thus, increase the local

The side-effects observed in this study were slight
and similar in the two groups. The frequency of these
side-effects is lower than in other studies [10], but this
difference can be partially explained by the absence of
systematic mycological study of the throat in our study.

The absence of a significant correlation between the
initial dose of oral corticosteroids and the sparing might
in part be caused by relative overdosage of oral steroids
at inclusion. It is not possible by addition of inhaled
steroids to a previous oral treatment, to determine
equivalent doses by the two routes since the degree of
change of oral prednisone was not related to the initial
dosage taken at D0. The attempt to identify clinical
features that predict response to the inhaled treatment
was not successful (FVC and age were the only
parameters which predicted response).

In summary, we have demonstrated that, in patients
with severe asthma requiring maintenance treatment with
oral corticosteroids, high-dose inhaled beclomethasone
dipropionate should be encouraged since: 1) it has a
substantial and often complete oral steroid-sparing
effect, not related to the initial dosage of oral steroids.
2) It allows a better control of airway obstruction with
a decrease of symptoms and causes few side-effects.

Acknowledgments: The authors gratefully acknowledge
the co-operation of the doctors who participated in this study: A.
Aram (Marseille), J. Bru (Caen), J. Bruno (Lyon), Ph Delaval
(Rennes), J.M. Dubois de Montreyraud (Reims), J. Germonty
(Limoges), P. Lebopote (Toulouse), J. Marsac (Paris), J.M.
Polu (Nancy), C. Sors (Paris), A. Tayard (Bordeaux), A.B.
Tonnell (Lille). Thanks are also due to Dr H. Boushey for
constructive criticism of the manuscript and to B. Rousselet
for typing the manuscript.

References
1. Brompton Hospital/Medical Research Council Collaborative trial. - Double-blind trial comparing two dosage
schedules of beclomethasone dipropionate aerosol in the
treatment of chronic bronchial asthma Lancet, 1974, ii, 303-
307.
2. Brompton Hospital/Medical Research Council Collaborative trial. - Double-blind trial comparing two dosage
schedules of beclomethasone dipropionate aerosol with a
placebo in chronic bronchial asthma. Br J Dis Chest, 1979,
73, 121-132.
3. Toogood JH, Lefcoe NM, Haines DSM, Jennings B,
Errington N, Baksh L, Chung L. - A grade-dose assess-
ment of the efficency of beclomethasone aerosol for severe
chronic asthma. J Allergy Clin Immunol, 1977, 59 (4), 298-
308.
4. American Thoracic Society. - Standards for the diag-
nosis and care of patients with chronic obstructive pulmon-
dary disease (COPD) and asthma. Am Rev Respir Dis, 1987, 136,
225-244.
5. Kalarus NC, Harrison AC. - Inhaled high-dose
beclomethasone in chronic asthma. NZ Med J, 1987, 100,
305-308.
budesonide in treatment of severe steroid-dependent asthma.
7. Tukianen P, Lahdensuo A. - Effect of inhaled
budesonide on severe steroid-dependent asthma. Eur J Respir
Dis, 1987, 70, 239-244.
8. Costello JF, Clark TH. - Response of patient receiving
high dose beclomethasone dipropionate. Thorax, 1974, 29,
571-573.
9. Smith MJ, Hodson ME. - High dose beclomethasone
inhaler in the treatment of asthma Lancet, 1983, 18319, 265-
269.
10. Tarlo SM, Broder I, Davies GM, Lezoff A, Mintz S,
Corey PN. - Six-month double-blind, controlled trial of high
dose, concentrated beclomethasone dipropionate in the treat-
ment of severe chronic asthma. Chest, 1988, 93, 998-1002.

RÉSUMÉ: Cent-vingt-quatre patients, atteints d'asthme sévère nécessitant un traitement d'entretien au moyen de corticostéroïdes oraux, ont été inclus dans une étude multicentrique randomisée en double aveugle, pour comparer les effets du dipropionate de beclomethasone en inhalation (BDP, 250 mcg par bouffée), en commençant par 1.000 mcg par jour, avec ceux d'un placebo (P). La fonction pulmonaire a été mesurée et les dosages de prednisone et de BDP (ou de P) ont été ajustés tous les 15 jours en tenant compte d'un score clinique. Après trois mois, nos observations montrent:

- Un taux d'abandon plus élevé dans le groupe P que dans le groupe BDP (36% versus 6% respectivement, p<0.01).
- L'abandon total de la prednisone chez 76% des patients du groupe BDP (dosage moyen de BDP = 1.270±340 mcg par jour, moyenne±écart type), versus 34% dans le groupe P (p<0.001).
- Le dosage quotidien moyen de prednisone a diminué de 17 mg±7.5 mg vers 3.1 mg±7.4 mg dans le groupe BDP versus 15.6 mg±7.7 mg à 9.1 mg±9.4 mg dans le groupe P (p<0.001) sans aucune relation entre l'effet d'épargne stéroïdien et la dose initiale de prednisone.
- Les variations moyennes du VEMS furent de +7±21% par rapport à la valeur initiale dans le groupe BDP, contre -6±20% dans le groupe P: p<0.01. Donc, chez des patients atteints d'asthme sévère nécessitant une corticothérapie orale, la BDP à forte dose a un effet d'épargne vis-à-vis des stéroïdes oraux très important, sans relation avec la dose initiale de stéroïdes oraux, et permet un meilleur contrôle de l'obstruction des voies aériennes que les seuls corticostéroïdes oraux.