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

J. Lacronique*, D. Renon**, D. Georges**, M. Henry-Amar***, J. Marsac*

High-dose beclomethasone: oral steroid-sparing effect in severe asthmatic patients. J. Lacronique, D. Renon, D. Georges, M. Henry-Amar, J. Marsac.
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^{-1}), 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^{-1}, 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 (FEV_1) 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.
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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 (FEV_1) 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.

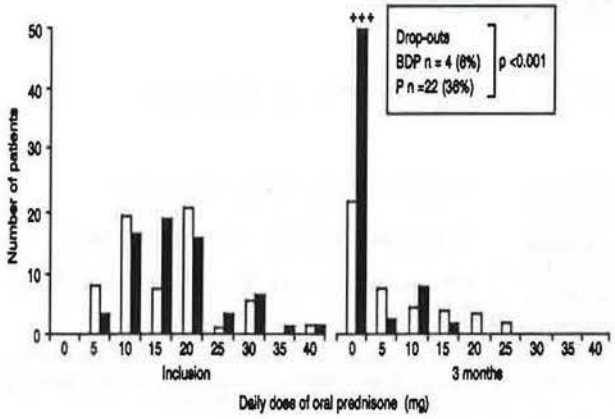

Fig. 1. – Distribution of the patients on inclusion (left) and at the end of the study period (right) according to the daily dose of prednisone (mg). +++: p<0.001; ■: beclomethasone dipropionate (BDP); □: placebo (P). The insert shows the drop-outs in the two groups of patients.

Each patient meeting the inclusion criteria was enrolled at day 0 (D0) after a run-in period of 15 days during which the patient was trained to use a peak flowmeter and a MDI correctly.

The investigator checked that the patient had regularly and correctly filled in his personal dairy. The patient was then assigned at random to BDP or P and given the inhaled MDI for treatment with BDP or P in a double-blind fashion. For each patient the initial daily dosage of BDP was 1,000 μg (250 μg, *q.i.d.*); all other medications were kept unchanged. All patients were asked to attend for regular checks by the same investigator in each centre every 14 days from D0 to D84.

Control of asthma was assessed by three different types of parameters: 1) Spirometric measurements were performed at the same time of day for each patient to avoid the effects of circadian changes in bronchial obstruction. Inhaled bronchodilator therapy was withheld 4 h before pulmonary function tests (PFT). The main objective criteria for asthma control was the measurement of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), before and 10 min after inhalation by MDI of two puffs of salbutamol (200 μg). 2) A standardized questionnaire evaluated the respiratory well-being using a vertical visual analogue scale (VAS) before measuring PFT to assess the patients' respiratory comfort or discomfort, scoring a 0 for the worst discomfort ("I've never breathed so badly") and 100 for the best control (I've never breathed so well"). The patient noted the following every day in his personal diary: the best value of three peak flow measurements measured in the morning (upon getting up) and evening (at bed time) before taking any asthma drug, the occurrence of attacks or respiratory discomfort, and the use of all other medications.

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 β_2-agonists but not by corticosteroids.
2) Occurrence of dyspnoea on a graded exertion, also requiring inhalation of β_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}, 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).

Table 1. – Patients' characteristics on inclusion

	BDP	P
N	63	61
Male	36	22
Female	27	39
Age yr	53±10	51±13
Age at onset of asthma yr	15±2	13±2
Current smokers %	6	3
Permanent respiratory discomfort %	40	28
PEF % pred	43±15	47±16
FEV_1 % pred	58±25	63±22
FVC % pred	80±24	85±25
Visual analogue scale (VAS) (100 mm line diagram)	59±26	58±25
Other medications used %		
$Beta_2$-agonist	97	95
Anticholinergics	27	21
Aminophylline	85	85
Daily dose of oral prednisone or prednisolone on inclusion mg	17.1±7.5	15.6±7.7

Data are presented as mean±SD. PEF: peak expiratory flow; FEV_1: 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. 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.

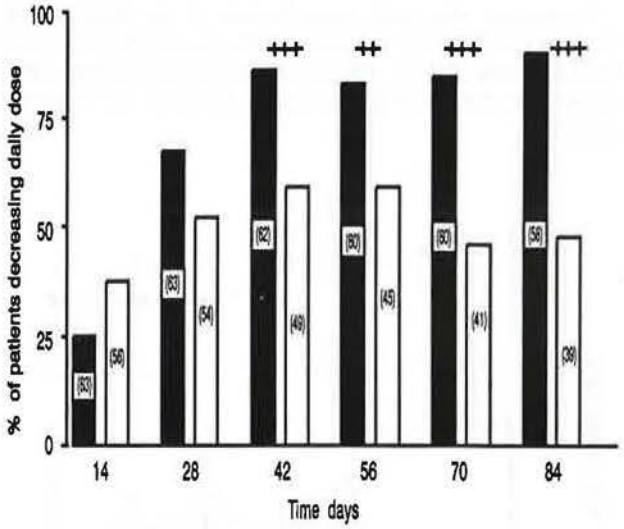

Fig 2. – Percentage of patients decreasing their dose of prednisone by 50% or more over the study period. **: $p<0.01$; ***: $p<0.001$. The number of patients remaining under study is given in parenthesis. ■ :beclomethasone dipropionate (BDP) n=63; □: placebo (P) n=61.

However, most patients (95%) in the BDP group with an initial dosage or oral corticosteroids lower than 15 $mg \cdot day^{-1}$ (class A) were completely weaned off oral corticosteroids, compared with 44% in the P group. For higher initial dosages (class B: 15–25 $mg \cdot day^{-1}$ and class C: >25 $mg \cdot day^{-1}$) 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 $\mu g \cdot day^{-1}$. 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 FEV_1 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 FEV_1 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 FEV_1, 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 FEV_1, the mean FEV_1 after salbutamol in the BDP group was maximum at D14 and did not change significant 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 FEV_1 and PEF was noticed throughout the study in both groups (r=0,63 to 0.73; $p<0.01$ from D14 to D84).

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 ($p<0.01$).

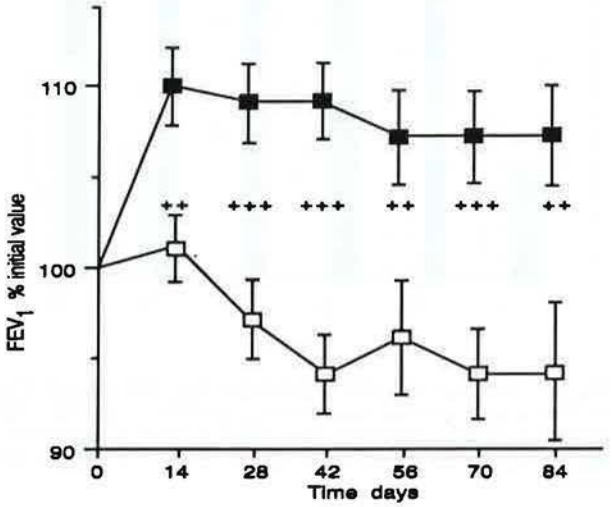

Fig. 3. – Mean values for FEV_1 (as % of initial values) over the study period (mean±SEM). **: $p<0.01$; ***: $p<0.001$; ■: beclomethasone dipropionate (BDP) (n=63); □: placebo (P) (n=61); FEV_1: forced expiratory volume in one second.

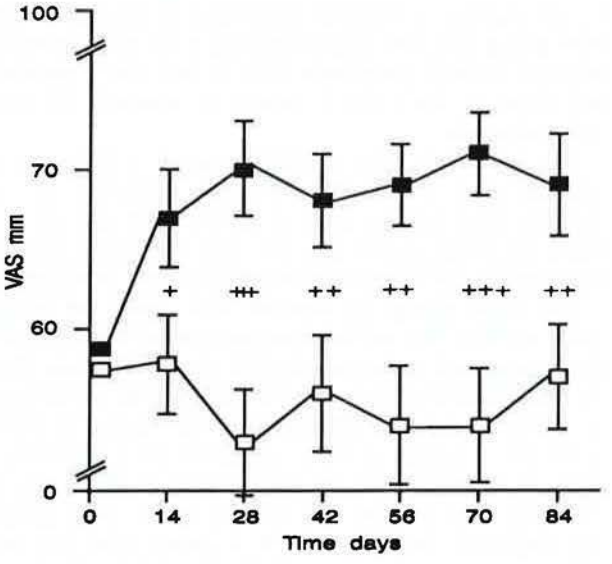

Fig 4. – Mean values of visual analogue score (VAS) (mm) over the study period (mean±SEM). *: $p<0.05$; **: $p<0.01$. ■: beclomethasone dipropionate (BDP) (n=63); □: placebo (P) (n=61).

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 D0 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 Toogood *et al.* [3] in patients poorly controlled by oral corticosteroids. With the MDI delivering 250 μg BDP·puff^{-1}, 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 beginning. This oral steroid-sparing effect of high doses of inhaled BDP was not unexpected. However, our observation 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 1±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 parameters enabling the assessment of the control of asthma (dyspnoea assessed by VAS or bronchial obstruction assessed by PEF) also showed that a significant difference 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 comparing 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 anti-inflammatory effect of steroid treatment.

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 equipotent 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.

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Beclomethasone à haute dose: effet d'épargne des stéroïdes oraux chez les patients asthmatiques graves. J. Lacronique, D. Renon, D. Georges, M. Henry-Amar, J. Marsac.

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±SD), *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.

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