

## First-time treatment with steroids in bronchial asthma: comparison of the effects of inhaled beclomethasone and of oral prednisone on airway function, bronchial reactivity and hypothalamic-pituitary-adrenal axis

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*First-time treatment with steroids in bronchial asthma: comparison of the effects of inhaled beclomethasone and of oral prednisone on airway function, bronchial reactivity and hypothalamic-pituitary-adrenal axis. W. Wilmsmeyer, D. Ukena, T.O.F. Wagner, G.W. Sybrecht.*

**ABSTRACT:** In a double-blind cross-over study of 12 asthmatic patients the effects of 1,000  $\mu\text{g}\cdot\text{day}^{-1}$  beclomethasone dipropionate (BDP) on airway function, bronchial reactivity and hypothalamic-pituitary-adrenal (HPA) axis have been compared to those of 15  $\text{mg}\cdot\text{day}^{-1}$  oral prednisone (PRD). None of the patients had ever received corticosteroids before. Fourteen days' treatment with either of both steroids improved airway function, both subjectively and objectively. Both steroids slightly reduced the responsiveness to histamine. PRD suppressed the corticotrophin-releasing factor (CRF) stimulated cortisol release more than BDP did, whereas there was no significant change in adrenocorticotrophic hormone (ACTH) release. The results indicate that short-term treatment with 1,000  $\mu\text{g}\cdot\text{day}^{-1}$  BDP reduces bronchial hyperreactivity (BHR) in asthmatic patients, whilst having subtle effects on HPA axis.  
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Hyperreactivity of the airways to a wide range of stimulants is a hallmark of asthma [1, 2]. There is increasing evidence that inflammation of the airways contributes to the hyperresponsiveness [1, 3, 4]. Glucocorticosteroids (GCS) remain the most effective therapy for asthma. The mechanism of action of GCS in asthma is still poorly understood, but is probably related to their anti-inflammatory properties. The steroids can be administered systemically, either by injection or orally, or by the inhaled route. Since introduction of the newer corticosteroid aerosols, it has been shown in numerous reports that control of asthma was improved and that aerosol treatment often permitted reduction in the doses of systemic steroids [5, 6]. On the other hand, the information about the effectiveness of steroids in reducing bronchial hyperreactivity (BHR) is less convincing. In some reports a reduction of nonspecific responsiveness was found by prolonged treatment with aerosolized preparations [5, 7-9], whilst in others no such effects have been found [10, 11]. Furthermore, when aerosols are used, reduction in symptoms or improvement in isolated measurements of lung function, rather than a decrease in the severity of BHR, has often been used as the goal of management.

Debate continues about the threshold dose of beclomethasone dipropionate (BDP), at which suppression of endogenous cortisol secretion is likely to occur [6, 12-17].

On the other hand, measurements of plasma cortisol concentrations do not allow a detailed analysis of disturbance in the hypothalamic-pituitary-adrenal (HPA) axis. The corticotrophin releasing factor (CRF) test has recently been introduced as a sensitive method for diagnosis of disturbance in the HPA axis [18, 19].

In the present study the effects of 1,000  $\mu\text{g}\cdot\text{day}^{-1}$  BDP on airway function, bronchial reactivity and HPA axis have been compared to those of 15  $\text{mg}\cdot\text{day}^{-1}$  prednisone in 12 asthmatic patients.

### Patients, methods and materials

Four female and eight male asthmatic patients, fulfilling the prerequisites for diagnosis [20] and ranging in age from 19-47 yrs, participated in the study. They were out-patients and performed normal duties throughout the study. The protocol of the study was approved by the hospital ethical committee and informed consent was obtained from all patients.

The anthropometric data and clinical characteristics of the patients are listed in table 1. The patients took their medication for at least three months on a regular basis. Values for forced expiratory volume in one second ( $\text{FEV}_1$ ) and peak expiratory flow rate (PEFR) are listed in

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table 2. All patients demonstrated reversibility of airway obstruction of at least 15% in FEV<sub>1</sub> after the administration of a β<sub>2</sub>-sympathomimetic by aerosol. None of the patients had ever received corticosteroids previously.

0.13–0.16 ml·min<sup>-1</sup>. Phosphate-buffered saline was inhaled first and was followed at 5 min intervals by doubling concentrations of histamine dihydrochloride. The response was measured by FEV<sub>1</sub> before and 1 min after

Table 1. – Clinical characteristics of the asthmatic patients

No.	Patient Sex	Age yrs	Height cm	Weight kg	Type of asthma		Concomitant medications
1	M	22	193	96	intr.	-	β
2	M	21	182	69	-	extr.	β, C
3	M	42	185	85	intr.	-	β, T
4	F	24	170	57	intr.	-	β, T, I
5	F	24	167	72	-	extr.	β, T, I
6	M	31	154	60	intr.	extr.	β, T
7	M	47	172	77	intr.	extr.	Keto
8	M	29	168	67	intr.	extr.	β, T
9	M	28	168	56	intr.	-	β
10	F	34	162	52	-	extr.	β, T, C
11	F	19	176	58	intr.	-	β, T
12	M	26	177	73	intr.	-	β, T, I

intr.: intrinsic; extr.: extrinsic; β: inhalative β<sub>2</sub>-sympathomimetic; C: disodium cromoglycate; T: theophylline; I: ipratropium bromide; Keto: ketotifen.

The study was performed according to a double-blind, cross-over design. After a five day run-in period, in which the patients continued their usual medication, the subjects were allocated at random to two groups. One group received 1 mg·day<sup>-1</sup> beclomethasone dipropionate (BDP), (Glaxo, FRG; 250 µg per puff twice in the morning and in the evening) plus placebo prednisone tablets, followed by prednisone tablets (15 mg between 6 a.m. and 8 a.m. before breakfast; Glaxo, FRG) and a placebo BDP aerosol for 14 days. The other group received these treatments in the reverse order. Each patient was instructed in the correct use of the pressurized aerosol. To avoid local side-effects from deposition of the steroid in the oropharynx, all patients were instructed to rinse their mouths after each aerosol treatment. The patients recorded PEFr in the morning and in the evening with a mini-Wright peak flow meter. Three readings were made each time, and the highest value was used for calculations.

Each patient was seen on entering the trial and at the end of each 14 day period. On these occasions, patients were evaluated by a review of their symptoms and medication scores, physical examinations, followed by measurement of PEFr, endocrinological measurements, spirometry (FEV<sub>1</sub> and forced vital capacity) and histamine inhalation test. The patients did not take any steroids on the day of examination. To avoid any interference with the histamine inhalation test [21], β<sub>2</sub>-adrenoceptor agonists were withheld for 8 h, and xanthenes for 24 h before the test.

#### Histamine inhalation test (HIT)

HIT was carried out according to the method of COCKCROFT *et al.* [22]. Aerosol was generated by a Wright nebulizer, delivered directly into a mask, held loosely over the mouth and clipped nose, and inhaled by tidal breathing for 2 min. Nebulizer output was maintained at

each inhalation. Inhalations were discontinued when there was a fall in FEV<sub>1</sub> of 20% or more below the lowest post-saline value. Concentration-response curves to histamine were plotted relating the percentage fall in FEV<sub>1</sub> to the logarithm of the cumulative dose of histamine inhaled. From these curves, the concentration that produced 20% fall in FEV<sub>1</sub> (PC<sub>20</sub>) was read by interpolation. Some subjects had a 20% fall in FEV<sub>1</sub> after inhalation of saline. In these cases, therefore, a PC<sub>20</sub> could not be calculated.

#### Endocrinological evaluation

The corticotrophin releasing factor (CRF) test is a novel, sensitive method for diagnosis of disturbances in the HPA axis [18, 19]. After two blood samples for basal values (-15 min and 0 min at identical times before breakfast) 100 µg CRF (hCRF-Bissendorf *i.v.*, Bissendorf, FRG) were injected within 60 s. No side-effects after CRF-application were observed. Further blood samples were obtained 15, 30, 45 and 60 min after injection. The plasma adrenocorticotrophic hormone concentration was measured by radioimmunoassay (INC-RIA Immuno-Nuclear Corporation, Stillwater, Minnesota, USA). Intra- and interassay coefficients of variation were 6% and 13%, respectively. The plasma cortisol concentration was determined by a fluorescence assay (Syva-Advance-Cortison-Assay, Syva Advance, Palo Alto, CA, USA). Intra- and interassay coefficients of variation were 6% and 9%, respectively. Areas under the plasma concentration *versus* time curves (AUC) were calculated as integrals under the polygon curves.

#### Statistics

The study was carried out according to HILLS and ARMITAGE [23] as a cross-over, clinical trial, in which the



Table 2. - Effects of beclomethasone or prednisone on FEV<sub>1</sub>, PEFR and PC<sub>20</sub> for histamine in asthmatic patients

No.	FEV <sub>1</sub>						PEFR (morning)						PEFR (evening)						PC <sub>20</sub>	
	C		BDP		PRD		C		BDP		PRD		C		BDP		PRD		C	BDP
	l	% pred	l	% pred	l	% pred	l	% pred	l	% pred	l	% pred	l	% pred	l	% pred	l	% pred	mg·ml <sup>-1</sup>	mg·ml <sup>-1</sup>
1	3.75	71	3.70	69	3.65	65	522	540	578	548	596	629	-	0.056	0.046					
2	4.05	72	4.50	79	4.30	75	560	584	566	600	611	611	0.328	0.066	0.064					
3	3.45	65	3.80	68	3.60	66	496	569	510	584	634	664	0.027	0.074	0.060					
4	3.30	87	3.40	94	3.30	87	352	354	434	428	399	439	0.099	0.308	0.078					
5	2.00	66	2.50	75	2.00	66	271	271	344	310	343	370	-	0.029	0.019					
6	2.25	66	2.55	73	2.40	73	382	348	382	386	411	463	-	0.045	0.031					
7	3.10	82	3.00	75	3.10	78	502	521	522	528	526	533	0.392	0.500	0.448					
8	3.30	69	3.30	65	3.30	66	490	565	565	562	593	599	0.062	0.046	0.097					
9	3.60	86	3.80	83	3.80	83	566	583	581	580	597	583	0.091	0.280	0.500					
10	2.30	66	2.20	69	2.35	69	382	373	378	388	394	380	0.025	0.039	0.035					
11	3.80	84	3.80	86	3.80	86	306	354	317	356	449	439	0.115	0.320	0.139					
12	2.50	66	3.10	66	2.95	70	414	452	447	464	513	504	0.031	0.047	0.043					

FEV<sub>1</sub>: forced expiratory volume in one second; PEFR: peak expiratory flow rate; PC<sub>20</sub>: provocative concentration producing a 20% fall in FEV<sub>1</sub>; C: control; BDP: beclomethasone dipropionate; PRD: prednisone.

effects of different treatments are compared on the same subject during different treatment periods. Data were analysed according to the method of HILLS and ARMITAGE [23] using the SPSS-X-programme of the Medizinische Hochschule Hannover.

## Results

The patients tolerated both short-term courses of corticosteroid therapy without any complaints. In particular, there were no problems with oropharyngeal candidiasis, hoarseness or sore throat during BDP therapy, probably due to careful rinsing of the mouth after each inhalation and the short duration of active medication. Regarding patient no. 2, the results of the histamine inhalation test and of the endocrinological tests were excluded from statistical analysis; on the day before the trial he took an antihistaminic drug and an oral glucocorticoid for symptoms of neurodermitis; these drugs would have interfered with the clinical tests. Patients' compliance was excellent, as carefully checked by the diary cards and by nebulizer weight (decrease: 4.32±0.44 g). Patients unanimously accepted both forms of therapy without any marked difference in preference.

The effect of steroid therapy on airways function is summarized in table 3. With both steroids there was a slight increase in FEV<sub>1</sub>, which was statistically significant for BDP. The effects of steroid therapy on PEFR were more pronounced. Compared to pretreatment values, both corticosteroids significantly increased PEFR values in the morning as well as in the evening. The increases in FEV<sub>1</sub> as well as in PEFR, induced by BDP and prednisone are not statistically significant from each other.

As shown by the increase in PC<sub>20</sub> values, treatment with both 1,000 µg·day<sup>-1</sup> BDP and 15 mg·day<sup>-1</sup> PRD leads to a reduction in bronchial reactivity (tables 2 and 3). Patients no. 1, 5 and 6 showed a 20% fall in FEV<sub>1</sub> after inhalation of saline and were, therefore, excluded from the statistical analysis, together with patient no. 2 (see above). There was an increase from the mean PC<sub>20</sub> of 0.069 mg·ml<sup>-1</sup> for the steroid-free period to values of 0.132 and 0.110 mg·ml<sup>-1</sup> for BDP and PRD therapy, respectively (table 3). This reduction in bronchial reactivity reached statistical significance for BDP therapy (p=0.01 versus control, table 3).

Finally, the effects of BDP and PRD treatment on the HPA-axis were studied. The plasma concentrations for cortisol and ACTH were in the normal range before the study. With both kinds of steroid treatment, there is a reduction in basal cortisol concentrations, although the values are still within the normal range and the differences do not reach statistical significance (fig. 1). No significant decrease in basal ACTH levels could be observed. After CRF administration, there was a statistically significant decrease in maximum cortisol concentrations; the effect of PRD was more pronounced than that of BDP, although this difference was not statistically significant. In contrast, neither steroid suppressed CRF-stimulated ACTH-release. Similar results



Table 3. - Effects of corticosteroid therapy on lung function in asthmatic patients

Drug regimen	FEV <sub>1</sub> l		PEFR l·min <sup>-1</sup>			PC <sub>20</sub> mg·ml <sup>-1</sup>	
		p	morning	p	evening	p	p
Pretreatment	3.12±0.20		438±28		478±29		0.069 (0.032-0.148)
BDP	3.30±0.19	<0.05	460±33	<0.05	506±30	<0.01	0.132 (0.055-0.315)
PRD	3.20±0.20	=0.05	468±28	<0.005	518±29	<0.005	0.110 (0.048-0.248)

Data for FEV<sub>1</sub> and PEFR expressed as mean±SEM, n=12; and for PC<sub>20</sub> as geometric means with 95% confidence limits in parentheses, n=8; BDP: beclomethasone dipropionate; PRD: prednisone; FEV<sub>1</sub>: forced expiratory volume in one second; PEFR: peak expiratory flow rate; PC<sub>20</sub>: provocative concentration producing a 20% fall in FEV<sub>1</sub>. Statistical significance was measured versus pretreatment values.

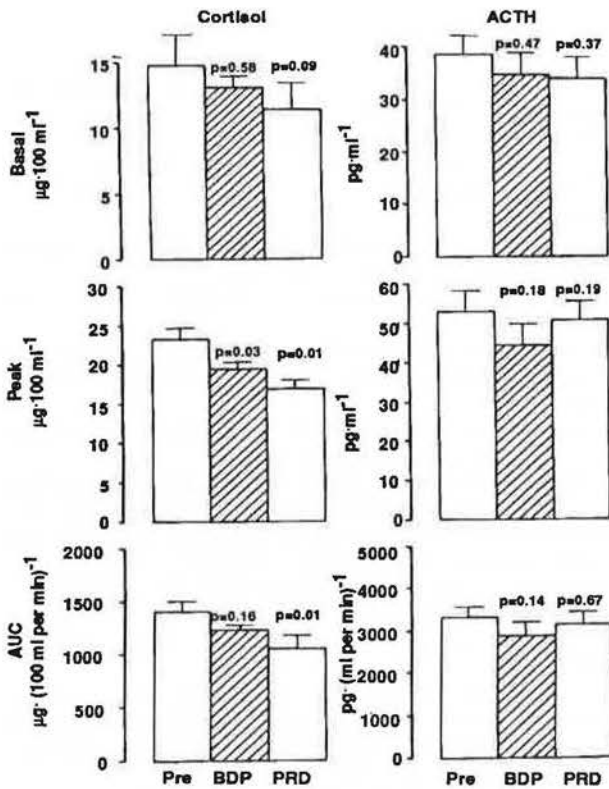


Fig. 1. - Plasma concentrations of cortisol and of ACTH after CRF injection. Values are mean±SEM from 9 (cortisol, patients 4 and 5 not included because of taking oral contraceptives) resp. 11 (ACTH) patients. Pre: pretreatment; BDP: beclomethasone dipropionate; PRD: prednisone; ACTH: adrenocorticotropic hormone; CRF: corticotrophin releasing factor; AUC: area under the plasma concentration-time curve. Statistical significance: treatment vs pretreatments.

were obtained by analysing the areas under the plasma concentration-time curves (AUC) for cortisol and ACTH after CRF injection. Again, PRD significantly suppressed AUC values for cortisol, whereas the effect of BDP was less pronounced. There was no change in AUC values for ACTH under BDP or PRD therapy.

**Discussion**

Bronchial hyperresponsiveness to a wide range of pharmacological and physical agents is one of the most

characteristic features of asthmatic airways. There is a relationship between the degree of bronchial responsiveness and the severity of symptoms in asthma [1, 2, 4]. Conversely, a reduction in bronchial responsiveness is associated with a reduction in asthmatic symptoms. Airway inflammation is probably the cause of BHR and, therefore, anti-inflammatory treatment is needed.

In the present study the effects of short-term treatment with inhaled BDP and oral prednisone have been compared to each other in 12 asthmatics. It should be pointed out that the study is not placebo-controlled. Based on the analysis for each individual, possible carry-over effects between the treatment periods were not found. The chosen doses of the drugs are quite common in clinical practice and are considered to be nearly equivalent, based on ventilatory function measurement. Treatment with either 1,000 µg·day<sup>-1</sup> BDP or 15 mg·day<sup>-1</sup> PRD for 14 days reduced BHR, as indicated by increases of the PC<sub>20</sub> values. Interestingly, at the doses administered in this study, BDP was slightly more potent than prednisone in reducing airway reactivity. The PC<sub>20</sub> for histamine increased about twofold after 14 days treatment with 1,000 µg·day<sup>-1</sup> BDP. A comparable improvement in the severity of BHR has also been described by KRAAN *et al.* [7] and RYAN *et al.* [24]. They found a decrease in BHR after 4 weeks' treatment with BDP or budesonide, respectively. In a recent study, an about seven-to eightfold increase in PC<sub>20</sub> for histamine after 3-4 weeks treatment with 800 µg·day<sup>-1</sup> BDP in patients with severe asthma was found [9]. The reason for these large increases in PC<sub>20</sub> in the latter study [9] compared to the present study and other studies mentioned above are not clear, but may be partially explained by the observation that some patients showed an up to 25-fold increase in PC<sub>20</sub> after 4 weeks of treatment [9].

Despite these differences in the degree of increase of PC<sub>20</sub>, all these studies show that there is an increase in the provocative dose of histamine needed to cause a 20% reduction in FEV<sub>1</sub>, indicating that aerosol corticosteroids do reduce BHR even after short-term treatment. The rather small changes in the severity of BHR after short-term treatment with BDP suggest that continued treatment with inhaled steroids is necessary to achieve a maximal improvement of patients. Thus, it is possible that regular long-term therapy with inhaled steroids allows healing of the asthmatic inflammation.



Both BDP and prednisone improved ventilatory function parameters in a significant manner, as indicated mainly by increases in PEF. As was the case for BHR, the degree of improvement was rather small after the short-term treatment. These results together with the reduction in BHR indicate that there is an objective benefit to treatment of patients with steroids, preferentially with aerosols.

One complication of steroid therapy that warrants emphasis is the suppression of the pituitary-adrenal axis. A very wide range of dosages has been reported for suppression of endogenous cortisol production by BDP [6, 14, 25]. Thus, the critical *per diem* dosage of BDP has variably been identified as 400, 800, 1,600, 2,000 and 3,000  $\mu\text{g}$  [6, 12–17]. Other reports cite no suppression over the range of 400–2,000  $\mu\text{g}\cdot\text{day}^{-1}$  [26, 27]. No change in morning cortisol levels was found after a one year treatment with 1,000  $\mu\text{g}\cdot\text{day}^{-1}$  BDP [28]. It has been suggested that systemic effects of BDP are of little or no practical importance unless the daily dose approximates to or exceeds 2  $\text{mg}\cdot\text{day}^{-1}$  [6]. GRANT *et al.* [29] found that any appreciable course of oral steroids at any time may have a long-term effect on basal adrenocortical activity. In preparing our study, we were very careful to select only patients who had never received any glucocorticosteroids previously. After 14 days' treatment with 1,000  $\mu\text{g}\cdot\text{day}^{-1}$  or 15  $\text{mg}\cdot\text{day}^{-1}$  PRD, there was a reduction in basal cortisol concentrations, particularly after PRD treatment, although the values were still within the normal range. Both PRD and BDP significantly reduced peak cortisol concentrations after CRF-stimulation, and PRD also significantly suppressed AUC values for cortisol. In contrast, there was no decrease in basal and CRF-stimulated ACTH release.

Following long-term corticosteroid therapy or short-term high-dose steroid therapy, hypothalamic-pituitary-adrenal function becomes suppressed. When steroid therapy is withdrawn from the patient with suppressed function, the patient is at risk for acute adrenal insufficiency [25]. The present results of the unchanged basal and CRF-stimulated ACTH release could indicate normal function of the pituitary, whilst reduced stimulated cortisol levels might suggest attenuated adrenal reserve. This does not mean, however, that the pituitary is necessarily normal with respect to stress response, as supramaximal CRF dosage was used [30]. The fact that cortisol secretion is reduced, in spite of an unchanged area under the concentration time curve of ACTH, demonstrates a reduced responsiveness at the adrenal rather than the pituitary level. It cannot be excluded, however, that the late phase of the concentration time curve would show some difference as blood samples were only collected for 60 min [31]. It appears, therefore, that not only long-term therapy, but also short-term therapy with BDP aerosol or low-dose oral PRD affect adrenal gland responsiveness. Alternatively, since the biological half-life of prednisone is 18–36 h, the reduced adrenal response after oral prednisone could also be due to maintained steroid activity on the gland from the oral dose given the day before.

The present study does not provide any information as to how long the effects observed would possibly last. This very important aspect of untoward effects of steroids (inhaled or oral) will have to be addressed carefully together with the question of whether the suppression becomes more pronounced with longer treatment. In view of the increasingly recommended high dosages of steroid aerosols, a detailed and careful analysis of the HPA axis after long-term therapy with steroid aerosols is necessary. Furthermore, the influence of long-term therapy with steroid aerosols on androgen production, which is potentially affected, needs to be studied [32].

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*Premier traitement aux stéroïdes dans l'asthme bronchique: comparaison des effets de la beclomethasone en inhalation et de la prednisone orale sur la fonction des voies aériennes, la réactivité bronchique, et l'axe hypothalamo-hypophyso-surrénalien.* W. Wilmsmeyer, D. Ukena, T.O. Wagner, G.W. Sybrecht.

RÉSUMÉ: Dans une étude en double aveugle avec permutation croisée chez 12 patients asthmatiques, l'on a comparé les effets de 1000 µg par jour de dipropionate de beclomethasone (BDP) sur la fonction des voies aériennes, la réactivité bronchique et l'axe hypothalamo-hypophyso-surrénalien, avec ceux de 15 mg par jour de prednisone orale (PRD). Aucun des patients n'avait reçu préalablement de corticostéroïdes. 14 jours de traitement au moyen des deux types de stéroïdes ont amélioré la fonction pulmonaire, à la fois subjectivement et objectivement. Les deux modes d'administration ont réduit légèrement la réactivité à l'histamine. La prednisone orale a entraîné une réduction du facteur libérateur de la corticotropine (CRF), et a stimulé la libération de cortisone plus que ne l'a fait le BDP, quoiqu'il n'y ait pas eu de modification significative dans la libération d'ACTH. Ces résultats indiquent qu'un traitement à court terme avec 1000 µg par jour de BDP réduit l'hyperréactivité bronchique des patients asthmatiques tout en n'ayant que des effets légers sur l'axe hypothalamo-hypophyso-surrénalien. *Eur Respir J.*, 1990, 3, 786-791.