

High-dose inhaled steroids in the management of asthma

A comparison of the effects of budesonide and beclomethasone dipropionate on pulmonary function, symptoms, bronchial responsiveness and the adrenal function

Svendsen UG, Frølund L, Heinig JH, Madsen F, Nielsen NH, Weeke B. High-dose inhaled steroids in the management of asthma. A comparison of the effects of budesonide and beclomethasone dipropionate on pulmonary function, symptoms, bronchial responsiveness and the adrenal function *Allergy* 1992; 47: 174–180.

The efficacy of budesonide (800 µg b.d.) and beclomethasone dipropionate (750 µg b.d.) in controlling the symptoms of asthma, pulmonary function, bronchial responsiveness to histamine, and adrenal function, was assessed in a double-blind, double-dummy cross-over study of 36 adult chronic asthmatic patients. The patients, the majority of whom were assessed to be affected to a severe degree, were insufficiently controlled in their current regimen of inhaled steroids and/or inhaled and oral bronchodilators. A 2 weeks baseline period preceded 6 weeks of treatment with each of the study drugs. Both treatment groups showed improvements from baseline in clinical assessment of lung function carried out after the first 6 weeks of treatment. No significant differences were seen throughout the entire 12 weeks study, when comparing the effects of the treatments on FEV₁, FVC, PEF or the histamine PC₂₀. Asthma severity, symptom score and inhaled bronchodilator use showed the same results after both treatments. It is concluded that inhalations of budesonide and beclomethasone dipropionate in high doses are equally potent in the treatment of severe asthma. There is no significant influence on the adrenal function and no significant side effects during a period equal to that of the present study.

U. G. Svendsen¹, L. Frølund²,
J. H. Heinig², F. Madsen², N. H. Nielsen²,
B. Weeke²

¹Department of Pulmonary Medicine, Gentofte County Hospital, and ²Medical Department TTA, State University Hospital, Copenhagen, Denmark

Key words: asthma; bronchial hyperresponsiveness; high doses, budesonide, beclomethasone; inhalation provocation tests

Ulrik Gerner Svendsen, M.D., D.Sc.
Dept. of Pulmonary Medicine Y
Gentofte County Hospital
Niels Andersenvej 65
DK-2900 Hellerup
Denmark

Accepted for publication 14 December 1991

Various corticosteroids are used topically in the treatment of asthma, but the majority of studies have been carried out with beclomethasone dipropionate (BDP), which has proved to be an effective and safe drug for most patients. The inhalation of corticosteroids is characterized by a high topical activity relative to systemic absorption, i.e. only a small dose needs to be delivered to the airways to achieve therapeutic activity, thus minimizing systemic absorption and unwanted side effects. In recent years, high-dose inhaled therapy with steroids have gained acceptance as a safe treatment for moderate and severe asthmatics, and it is generally believed that no significant adrenal suppression is observed with the doses normally used. However, local complications such as oropharyngeal candidiasis and dysphonia have been observed. The aim of the present study was to compare the effects of 2 well-known steroids which are now available for high-dose inhalation therapy, viz. budesonide and beclomethasone dipro-

pionate. Such comparisons are important when the clinical alternative to high-dose inhalation therapy might be oral steroids with a high frequency of serious side effects. Compared to former studies (1) the present study, besides estimations of symptom score, pulmonary function, daily medicine use, and adrenal function, also includes a comparison of the effects on bronchial responsiveness and the incidence of oral candidiasis.

Study population and methods

Thirty-nine asthmatic patients (2) of either sex, aged 18 years and older, referred from other hospitals or general practitioners, were selected for the study. Their asthma was poorly controlled by inhaled steroids with daily doses in the usual range of 300 µg to 500 µg given by a standard dose inhaler. Patients had perennial reversible airways obstruction, and the lung function (FEV₁, FVC or PEF) was either

<70% of the predicted normal value (3) at inclusion, or at least 50% of the morning and evening PEF measurements in the run-in period were <70% of the predicted normal values. Further, at least 15% reversibility of FEV₁ should be demonstrated at the inclusion 10 min after inhalation of 200 µg of salbutamol via an inhaler, or a spontaneous variability in PEF of 20% or more should be measured over a 4 weeks observation period within the last 6 months prior to the study. All patients should have an increased bronchial responsiveness to inhaled histamine upon entry in the study with a PC₂₀ histamine (4) value (i.e. the provocative concentration of histamine causing a 20% fall in FEV₁) <2 mg/ml. Thirty patients were smokers, 2 had stopped smoking more than 6 months before the study. Atopic patients, i.e. patients in whom skin prick tests and/or radioimmunoallergosorbent tests (RAST) were positive to one or more commonly occurring allergens, and non-atopics were included. All patients were in evident clinical need (i.e. dyspnoea and wheeze despite inhaled steroids and bronchodilators when necessary) of additional anti-asthmatic treatment in addition to β_2 -agonists and/or theophyllines and standard doses of inhaled steroids (i.e. 300–500 µg daily), and all gave their informed consent. The study was approved by the local Ethics Committee. Excluded were patients currently taking regular oral corticosteroids or having taken oral steroids during the last 3 months, or for longer than 3 months during the last 12 months; patients unable to use the aerosols correctly; pregnant women; breastfeeding women; patients with significant renal, hepatic or cardiovascular disease, and patients having experienced respiratory infections within 4 weeks prior to the start of the study. The pollen-allergic patients had the study performed outside the season.

All patients were given a diary card at visit 1, and were observed at baseline for 2 weeks until visit 2 on 400 µg of inhaled BDP daily and inhaled β_2 -agonists and/or oral β_2 -agonists and/or theophyllines. After the successful completion of this baseline period (visit 2, week 0), the patients were randomly assigned to the treatment groups. They were requested to keep oral bronchodilator usage constant throughout the study. One group of patients started treatment with 1600 µg of BUD daily (i.e. 4 puffs of 200 µg b.d.) from a metered dose aerosol with an inhaler attachment "inhalette" system with a volumen around 150 ml, and also used placebo beclomethasone dipropionate aerosol. The other group received 1500 µg of beclomethasone dipropionate daily (i.e. 3 puffs of 250 µg b.d.) and placebo budesonide. Treatment was given for 6 weeks, and thereafter a cross-over of treatments was performed. Diary cards were filled in daily by the patients throughout the study, and the patients were seen in the clinic after

every 3 weeks of treatment. Altogether, patients made 6 visits for assessment. Visits 1 and 2 took place as mentioned, visits 3 and 4 at the half-way and final stages of treatment period 1, and visits 5 and 6 at the half-way and final stages of treatment period 2. Symptoms were recorded on a 0–4 scale (4 worst), for sleep, wheezing, activity restriction, cough, and phlegm. The patients also recorded their morning and evening PEF (Mini Wright peak flow meter, Airmed, Harlow, England), best of 3 measurements, measured 15 min after inhaled β_2 -agonists, and their daily consumption of both test treatment and, if needed, inhaled salbutamol (Ventoline®, Glaxo, UK). Before and after administration of the trial treatment, a laboratory monitoring was performed including haemoglobin, white cell count, platelet count, eosinophils, bilirubin, alkaline phosphatase, creatinine and electrolytes, and the urine was tested for presence of blood, protein and sugar. Only patients with "overall" results in the first test within "normal limits" were included. To assess the adrenal function, a short tetracosactrin test was performed before and after each 6 weeks' treatment period (with 250 µg of tetracosactrin intravenously and a repeated plasma cortisol determination after 30 min).

At all the clinical visits, measurements of FEV₁, FVC, PEF, PC₂₀ histamine, the asthma severity (based on the information in the diary cards) and throat swabs for *Candida* were performed. At the end of each treatment period, patients' "overall opinion" was obtained (i.e. how effective they thought the treatment had been ranging from "very effective" (= 1) to "made condition worse" (= 5)).

Prior to bronchial histamine challenge (and spirometry) the patients refrained from slow-release theophyllines for 48 h, plain theophyllines for 24 h, β_2 -agonists pressurized aerosols or rotacaps, budesonide or beclomethasone dipropionate for 6 h. Bronchial challenge was performed using tidal volume breathing of aerosols delivered by a Wright nebulizer with mouthpiece as described previously (5).

Statistical models

The lung function variables FEV₁, FVC, PEF, ln PC₂₀ and the diary card variables were analysed and compared using the tests for comparisons of 2-period cross-over clinical trials (6, 7, 8). Only the second half of each treatment period was analysed to avoid carry-over effects; the lung function data used were obtained at visits 4 and 6, and the diary card data used were mean daily scores over the periods between visits 3 and 4 and between visits 5 and 6. The analyses and comparisons were all based on normal theory. However, the data on all lung function variables, the peak flows and salbutamol used appeared

to be reasonably symmetrical, but the score data were all right-skewed, suggesting that the normal analyses will be approximate. Consequently, non-parametric (Mann-Whitney) tests were also carried out to compare the 2 treatments (although this test does not correct for period or group effects).

The treatment preferences expressed by both patients and doctors (those expressing no preference have been excluded) were analysed using Gart's test (7), and similarly, this test was also used to look for period (i.e., is period 2 different from period 1?) effects.

As these methods might have some shortcomings, as discussed previously (5), it was additionally chosen to generalize the t-tests by combining the data in a general linear model where the dependence of time is described by polynomials in time, and *polynomial regressions* (of 4th degree) were carried out. Parallel analyses were made on the basic variables PC_{20} , FEV_1 , FVC and PEF. Since PC_{20} varies over several orders of magnitude, it was decided to include the natural logarithm of PC_{20} in the study. Using this model 77–80% of the variation in the dependent variable could be explained ($R^2_{FEV_1} = 88.9\%$, $R^2_{FVC} = 86.9\%$, $R^2_{\ln PC_{20}} = 76.5\%$, $R^2_{PEF} = 91.2\%$) by the model. The *effect of a drug in the first period* was defined as the mean difference between the level at the end of the period and the beginning of the period. With the given model, this term is independent of the individual patient parameters.

All statistical tests were carried out at a 5% level of significance.

Results

Due to non-cooperation, a respiratory tract infection and throat irritation, respectively, 3 patients were excluded very early in the trial. Thus, a total of 37

Table 1. The mean and standard deviation (SD) of the quantitative variables obtained at visit 2 ($n_1 = n_2 = 20$)

	BDP-BUD		BUD-BDP		Overall
Age (yr)	44.6	(12.1)	47.7	(15.1)	46.2 (13.6)
Height (cm)	167.7	(7.8)	168.9	(7.9)	168.3 (7.8)
Weight (kg)	70.6	(13.6)	67.3	(13.4)	69.0 (13.5)
Duration of asthma (yr)	19.6	(15.7)	17.8	(13.7)	18.7 (14.6)
FEV_1 (l)	1.65	(0.74)	1.70	(0.99)	1.68 (0.86)
FVC (l)	2.52	(0.87)	2.70	(1.20)	2.61 (1.04)
PEF (l/min)*	311.9	(96.4)	310.8	(132.9)	311.5 (111.0)
PC_{20} (mg/ml)	0.218	(0.219)	0.569	(0.919)	0.393 (0.683)

* $n_1 = 18$; $n_2 = 13$ (where 1=BDP-BUD, 2=BUD-BDP).

patients have been included in the analysis. Patient characteristics are summarized in Table 1. Asthma severity was considered to be moderate in 11 patients, severe in 22 patients, and very severe in 4 patients, and was classified as extrinsic in 25 patients. No differences in these parameters were observed between treatment groups. All patients were *within* the normal range for the blood test variables before and after the test treatments, except for eosinophilic cells in the peripheral blood, which for 25 patients were above the normal range at the end of the baseline period.

Pulmonary function. The differences in the 4 basic parameters from the time of inclusion until the start of treatments were compared, and no significant differences were found. Table 1 shows the mean and standard deviation at visit 2, and no differences between the treatment groups were seen.

To test the treatments for efficacy, the withdrawn patients were not considered, resulting in a sample size of 36 in each arm of the study. Table 2 shows the results of the analysis of the lung function and diary card data. No differences between the

Table 2. Analysis of quantitative variables. n = number of patients in the treatment groups (either 'BDP' or 'BUD') used in the comparison. The least significant difference column shows the smallest difference between means that would prove to be significant at 5%. No important differences were found.

Variables	$n_1 = n_2$	Mean		Least significant difference	P-value		
		BDP	BUD		Group	Treatment	Period
FEV_1 (l)	35	1.808	1.848	0.176	0.83	0.65	0.95
FVC (l)	35	2.797	2.885	0.216	0.73	0.42	0.97
PC_{20} (mg/ml)	35	0.728	0.925	0.586	0.33	0.50	0.29
PEF (l/min)	24	345.00	368.00	23.11	0.70	0.19	0.61
Sleep	36	0.344	0.358	0.096	0.44	0.77	0.06
Wheeze	36	0.471	0.596	0.163	0.55	0.13	0.24
Activity restriction	36	0.490	0.574	0.151	0.80	0.25	0.50
Cough	36	0.502	0.558	0.175	0.70	0.52	0.06
Phlegm	36	0.509	0.581	0.175	0.87	0.41	0.06
AM PEF	36	321.75	318.11	11.71	0.49	0.53	0.50
PM PEF	36	337.60	336.61	12.55	0.49	0.87	0.27
Salbutamol use/day	36	6.938	7.580	0.968	0.53	0.19	0.03

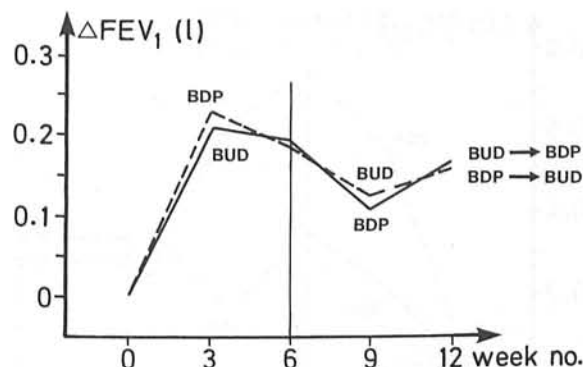


Fig. 1. Changes in FEV_1 . Starting point, 0, on the ordinate = the mean level for all patients at the beginning of treatment. After 6 weeks of treatment, a cross-over is made (vertical line), and the alternative treatment is administered. The solid curve = patients starting treatment with BUD and ending with BDP. The dotted curve = patients with the reversed order of medication. After 6 weeks of treatment no significant difference between the groups was observed.

treatment groups were seen (Table 2, p-value "Treatment"). The "least significant difference" column shows the smallest difference between means that would turn out to be significant at 5%. P-values are also given in Table 2 for group (i.e. tests for carry-over effects) and period (i.e., is period 1 different from period 2?) effect, and no significant differences were observed.

The analyses presented in Table 2 are based on normal theory, but, as mentioned above, non-parametric (Mann-Whitney) tests were also carried out to compare the 2 treatments (although this test does not correct for period or group effects). No

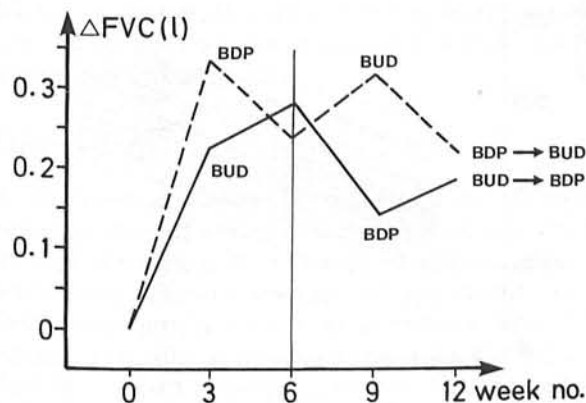


Fig. 2. Changes in FVC. Starting point, 0, on the ordinate = the mean level for all patients at the beginning of treatment. After 6 weeks of treatment, a cross-over is made (vertical line), and the alternative treatment is administered. The solid curve = patients starting treatment with BUD and ending with BDP. The dotted curve = patients with the reversed order of medication. After 6 and 12 weeks of treatment no significant difference between the groups was observed.

significant results were found from the Mann-Whitney test.

By *polynomial regression analysis* the effects on the pulmonary function and bronchial responsiveness of the 2 drugs were compared, and the results are shown in Table 3. It is seen that no significant differences are observed in either FEV_1 , FVC, PEF or in $\ln(PC_{20})$. An increase compared to baseline was observed in all the parameters in the first treatment period, which reached significance with both drugs in PEF. Neither in the first nor in the second treatment period were any differences observed between the effects of the drugs. Both drugs were generally able to maintain the increases in pulmonary function obtained by the other drug in the first period. No important carry-over effects were observed (Figs. 1–4).

Adrenal function. The adrenal function was assessed both by measuring the plasma cortisol level at visits 2, 4, and 6 (which all took place at approximately the same time of day) and by a short tetracosactrin test at the same visits.

No significant differences were observed between the level of plasma cortisol in the 2 groups (Fig. 5), and no significant differences were observed in the levels of plasma cortisol and in the results of the tetracosactrin tests after both treatments (Figs. 6 and 7).

Treatment preferences. No significant effects were found (the p values are 0.29 for both treatment and period effects for patient's preference and 0.22 and 0.82, respectively for treatment and period effects for doctor's preference).

Table 3. Effects, i.e. changes of different parameters following treatment with BDP and BUD, the observed levels of significance and carry-over effect. The lines BDP-BUD give the differences between the 2 drugs.

Variable	Drug	Total Effect	Effect Period 1	Effect Period 2	Carry-over
$\ln PC_{20}$	BDP	0.378*	0.741**	0.013	0.727*
	BUD	-0.081	0.360	-0.523*	-0.883*
	BDP-BUD		0.381	-0.537	
FEV_1 (l)	BDP	0.07	0.18	-0.03	0.22
	BUD	0.08	0.19	0.03	-0.22
	BDP-BUD		-0.01	0.00	
FVC (l)	BDP	0.07	0.24	-0.09	0.33
	BUD	0.13	0.28*	0.02	-0.30
	BDP-BUD		-0.04	-0.07	
PEF (l/min)	BDP	6.1	35.3**	-23.2	58.4**
	BUD	28.3**	49.5**	7.2	-42.3*
	BDP-BUD		-14.2	-30.4	

*** corresponds to significance at level 0.1%, ** to level 1%, and * to level 5%

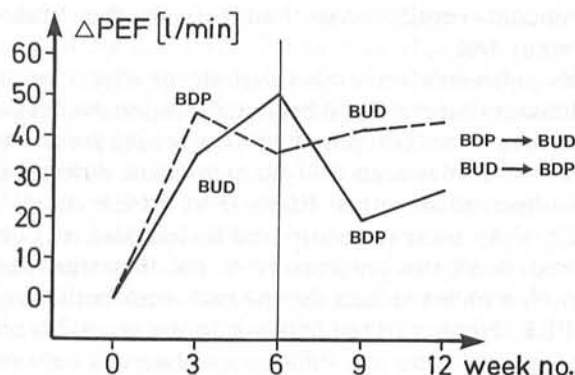


Fig. 3. Changes in PEF. Starting point, 0, on the ordinate = the mean level for all patients at the beginning of the treatment. After 6 weeks of treatments, a cross-over is made (vertical line), and the alternative treatment is administered. The solid curve = patients starting treatment with BUD and ending with BDP. The dotted curve = patients with the reversed order of medication. After 6 and 12 weeks of treatment no significant difference between the groups was observed.

Candida infections were noted in 7 patients (3 and 4 in each treatment group) during low-dose BDP treatment after the run-in period. After 6 weeks of treatment, an increase in positive *Candida* swabs were seen, i.e. 15 patients had positive swabs in the BDP

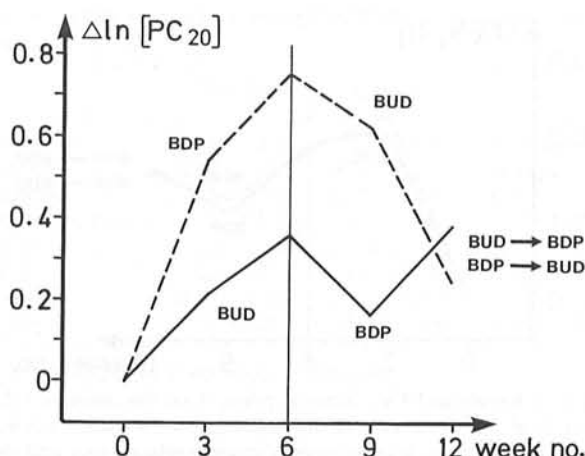


Fig. 4. Changes in $\ln PC_{20}$. Starting point, 0, on the ordinate = the mean level for all patients at the beginning of the treatment. After 6 weeks of treatment, a cross-over is made (vertical line), and the alternative treatment is administered. The solid curve = patients starting treatment with BUD and ending with BDP. The dotted curve = patients with the reversed order of medication. After 6 and 12 weeks of treatment no significant difference between the groups was observed.

treatment period, and 19 in the BUD treatment period ($p > 0.05$). Only one patient had symptoms due to *Candida*, i.e. sore throat, etc.

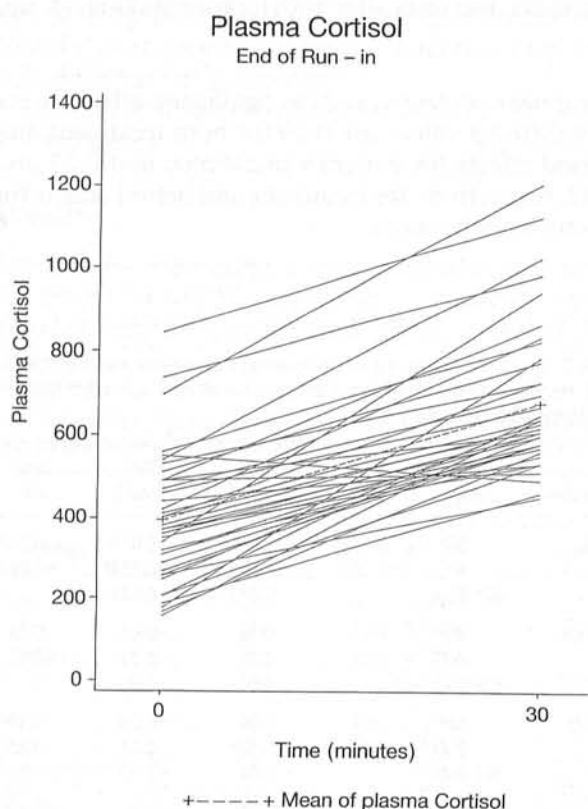


Fig. 5. Level of plasma cortisol (nmol/l) at the end of the run-in period in the study population. The range of measurements is within the normal. A normal increase in plasma cortisol is observed 30 min after administration of tetracosactrin.

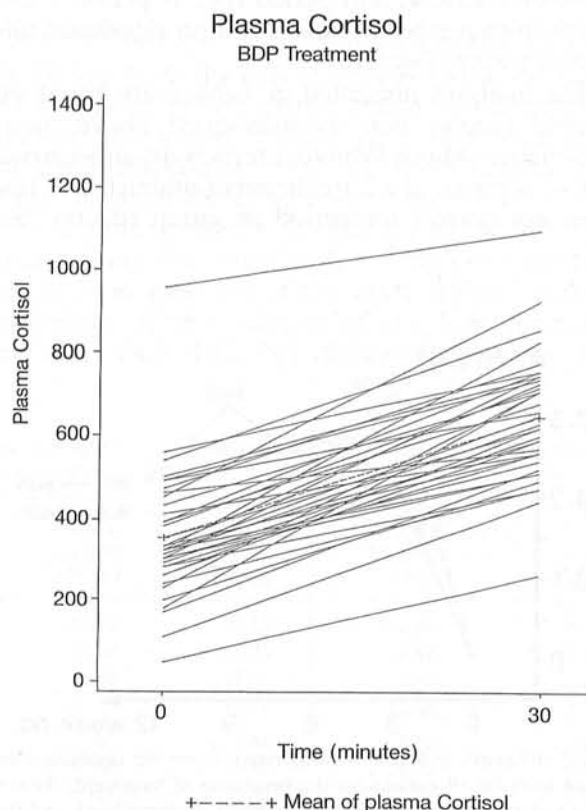


Fig. 6. Level of plasma cortisol (nmol/l) after 6 weeks of treatment with BDP (1500 $\mu\text{g/day}$). No significant difference is observed when compared to the level before start of the treatment (Fig. 5). A normal increase in plasma cortisol is observed 30 min after administration of tetracosactrin.

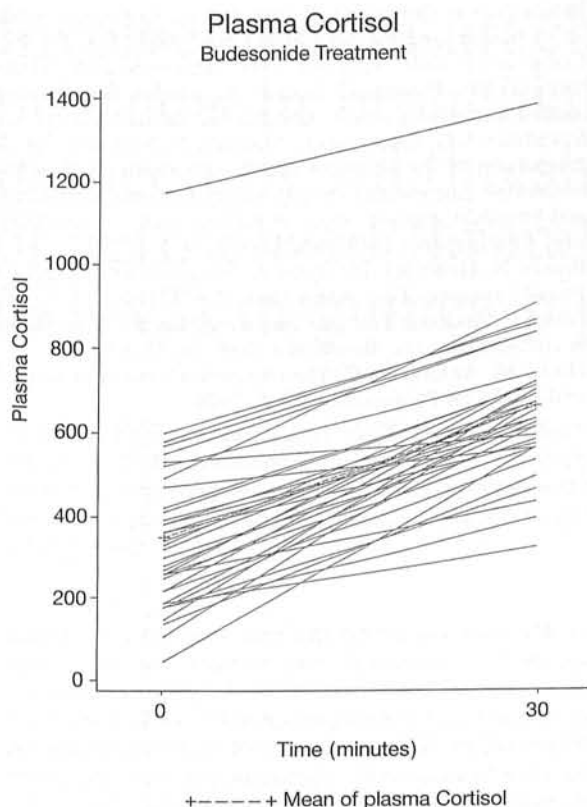


Fig. 7. Level of plasma cortisol (nmol/l) after 6 weeks of treatment with BUD (1600 µg/day). No significant difference is observed when compared to the level before start of the treatment (Fig. 5). A normal increase in plasma cortisol is observed 30 min after administration of tetracosactrin.

Unusual symptoms. The major drug-related comments concerned cough (16 patients during BUD treatment, 16 during BDP), irritation in the throat (10 during BUD, 7 during BDP), nausea (1 during BUD, 4 during BDP), acne (2 during BDP), hoarseness (1 during each treatment) and weight gain (1 during each treatment).

Discussion

As in previous studies (1), we have found no differences between the effects of the 2 steroids available for high-dose inhalation therapy in asthma, either in pulmonary function assessed by spirometry, or in daily symptoms, and no differences were seen in the adrenal function as evaluated by both plasma cortisol and a short tetracosactrin test. As expected, no differences were seen between the 2 drugs on the pulmonary sensitivity to histamine. Based on these observations, we have concluded that both drugs are highly effective in the management of moderate to severe asthma, and the clinical choice of drug should be based on other parameters, e.g. doctor's experience, patient preference, or cost in the country in

question. The small number of patients may have caused a difference to be overlooked, however, as stated in Table 2 in the column "least significant difference", the highest difference in FEV₁ which could have been overlooked was 0.176 l, and this difference was below the level which we consider to be of clinical significance after 6 weeks of high-dose inhalation therapy with steroids. No studies have documented clinically important differences between the 2 steroids and the chemistry of the drugs make such differences unlikely. It was impressive that despite the fact that an inhaler device was used in the budesonide treatment, this was not followed by a greater objective or subjective effect, and similarly, the frequency of positive oral *Candida* swabs was not lowered. However, with a greater number of patients differences might have been found. It was an important finding that the number of clinically important Candidiasis cases was extremely low ($n = 1$), again focusing on the safety of the drugs at least in short-term experiments like the present one. Many patients complained of cough, irritation in the throat, hoarseness and nausea. Again, no differences between treatments were seen, but local side effects may now be expected as inevitable in high-dose inhalation of steroids in asthma. Two patients complained of weight gain. Retrospectively, it was a mistake not to have included body weight in such a study as this. It may be tentatively concluded that steroidal side effects may occur in individual patients when doses of inhaled steroid are in excess of 1000 µg/day. With the tests used for assessment of adrenal function, no differences between the treatments were observed, and also no important influences on the adrenal function. This may either reflect the safety of the treatments, or the problematic nature of the tests used. Some workers prefer the insulin stress test, but until now no agreement on the matter has been achieved. Also, no normal values for the measure of adrenal function in asthmatic patients who have not taken steroids are available at present. The insulin stress test is an important test of the adrenal-pituitary axis. It cannot be performed as a routine procedure, but it certainly provides information on the whole axis. As shown in Fig. 5, a non-significant decrease in plasma cortisol is found after commencement of treatments, but a later normalization seems to occur.

It is concluded that budesonide and beclomethasone dipropionate are equally effective in high-dose inhalation therapy, and no important side effects were seen in the present short-term experiment. It seems, based on few clinical observations, that individual steroidal side effects may be observed in some patients when doses of inhaled steroids cross an unknown, individual border, probably above 1000 µg/day.

Acknowledgement

The authors are grateful to Docent Knut Conradsen, Institute of Mathematical Statistics and Operation Research, the Technical University of Denmark, for performing the statistical analysis and for many fruitful discussions in that connection.

References

- EBDEN P, JENKINS A, HUSTON G, DAVIES BH. Comparison of two high dose corticosteroid aerosol treatments, beclomethasone dipropionate (1500 µg/day) and budesonide (1600 µg/day), for chronic asthma. *Thorax* 1986; 41: 869-74.
- SCADDING JG. Definition and clinical categories of asthma. In: CLARK TJH, GODFREY S, eds. *Asthma*. London: Chapman & Hall, 1977: 1-11.
- BERGLUND E, BIRATH G, BJURE J, et al. Spirometric studies in normal subjects. *Acta Med Scand* 1953; 173: 185-92.
- COCKCROFT DW, KILLIAN DW, MELLON JJA, HARGREAVE FF. Bronchial reactivity in inhaled histamine: a method and clinical survey. *Clin Allergy* 1977; 7: 135-43.
- SVENDSEN UG, FRØLUND L, MADSEN F, NIELSEN NH. A comparison of the effects of nedocromil sodium and beclomethasone dipropionate on pulmonary function, symptoms, and bronchial responsiveness in patients with asthma. *J Allergy Clin Immunol* 1989; 84: 224-31.
- BAKER N, HEWS RJ, HUITSON A, POLONIECKI J. The Two Period Crossover Trial. *BIAS* 1982; 9: 67-116.
- GART JJ. An Exact Test for Comparing Matched Proportions in crossover designs. *Biometrika* 1969; 56: 75-80.
- HILLS M, ARMITAGE P. The two-period cross-over clinical trial. *Br J Clin Pharmacol* 1979; 8: 7-20.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.