

Effects of budesonide by means of the Turbuhaler on the hypothalamic-pituitary-adrenal axis in asthmatic subjects: A dose-response study

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Background: As a general phenomenon, corticosteroids may suppress the activity in the hypothalamic-pituitary-adrenal (HPA) axis. The adrenal stimulation test is a commonly used method to assess the relative risk of exogenous corticosteroids to induce systemic side effects.

Objectives: This clinical trial was performed to assess the effects of budesonide on the HPA axis (at 800, 1600, or 3200 µg/day, given as a twice daily regimen, administered by means of the Turbuhaler) in adult patients with mild, non-steroid-dependent asthma.

Methods: Sixty-four asthmatic patients received budesonide or placebo by inhalation or 10 mg/day oral prednisone once daily as a positive control in a double-blind, double-dummy, randomized, placebo-controlled, parallel-group, multicenter study.

Plasma cortisol concentration was measured to assess the effect on the HPA axis before and during a 6-hour infusion of synthetic adrenocorticotrophic hormone (ACTH), cosyntropin.

Results: After 6 weeks of treatment, plasma cortisol concentrations after adrenal stimulation by cosyntropin infusion had fallen by 4% in the placebo group; by 13%, 11%, and 27% in the budesonide groups (800, 1600, and 3200 µg/day, respectively); and by 35% in the prednisone group. The decrease was significant only in the 3200 µg/day budesonide ($p = 0.03$) and prednisone ($p = 0.005$) groups. Over the same time period, decreases in basal plasma cortisol concentrations were 1% in the placebo group; 19%, 19%, and 34% in the three budesonide groups; and 37% in the prednisone group. Only in the prednisone group was the decrease significant ($p = 0.03$ vs placebo).

Conclusions: In this study budesonide inhaled by means of the Turbuhaler, at doses recommended for clinical use (800 or 1600 µg/day), did not produce any statistically significant suppression of the HPA axis compared with placebo. (J Allergy Clin Immunol 1998;101:312-9.)

Key words: Asthma, budesonide, Turbuhaler, HPA axis, corticosteroids

Abbreviations used

ACTH:	Adrenocorticotrophic hormone
ANOVA:	Analysis of variance
HPA:	Hypothalamic-pituitary-adrenal
pMDI:	Pressurized metered-dose inhaler

Corticosteroids have, over the past 40 years, been the most effective therapy available for the treatment of asthma. However, the use of oral corticosteroids has been limited to patients with severe asthma because of the high incidence of systemic side effects. The incidence of such side effects has been reduced by administration of corticosteroids by inhalation. An improved ratio of local-to-systemic effects can thus be achieved because inhaled agents act locally, allowing lower doses of corticosteroid to be administered.¹ Consequently, inhaled corticosteroids can now partly or completely replace oral corticosteroids in the treatment of both severe and moderately severe asthma.

Budesonide was designed to enhance the topical antiinflammatory action and minimize the systemic side effects typical of other corticosteroids. Studies with budesonide, both preclinical and clinical, have demonstrated a favorable ratio between topical antiinflammatory activity and systemic corticosteroid effects over a wide range of doses.²⁻⁷ The low systemic activity of budesonide can be attributed to its rapid and extensive hepatic metabolism into metabolites with low intrinsic corticosteroid activity.^{8,9}

Like other corticosteroids, budesonide has been reported to cause dose-related suppression of plasma cortisol concentrations, which suggests that it may suppress activity in the hypothalamic-pituitary-adrenal (HPA) axis by inhibition of pituitary secretion of adrenocorticotrophic hormone (ACTH).¹⁰ This in turn would then depress the activity of the adrenal cortex and thus the levels of circulating cortisol.

Results from studies comparing the effects of inhaled budesonide and inhaled beclomethasone dipropionate and fluticasone suggest that budesonide has less of a suppressive effect on the HPA axis on a microgram-to-microgram basis.¹⁰⁻¹² Adrenal stimulation, with the use

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of ACTH or synthetic substitutes such as cosyntropin, is commonly used to assess HPA axis function. The ability of the adrenal gland to produce and secrete cortisol after ACTH stimulation is measured by determination of plasma cortisol concentrations. ACTH stimulation can be achieved by either a bolus injection of cosyntropin, followed by the measurement of plasma cortisol response 30 and/or 60 minutes after injection, or a 6- to 8-hour infusion of cosyntropin with 2-hour measurements of plasma cortisol concentration. The continued infusion is considered to be more reliable in determining the normal capacity of the adrenal glands to secrete cortisol because the elicited response is far greater than that found after a bolus injection.¹³ This has led one division at the Food and Drug Administration to recommend the continuous 6-hour ACTH infusion test as part of New Drug Applications for new steroid formulations for inhalation. Recently, this test has been used to evaluate the systemic effect of several inhaled corticosteroids in clinical studies in which treatment durations of 4 weeks have been used.¹⁴⁻¹⁷

The Turbuhaler (Astra Draco, Lund, Sweden) is an inspiratory flow-driven, metered-dose, dry-powder inhaler. The administration of budesonide by means of the Turbuhaler has been shown to give a lung deposition approximately twice that of a pressurized metered-dose inhaler (pMDI), with less variability.¹⁸ The principal objective of this study was to investigate the systemic effects (measured as plasma cortisol after a 6-hour cosyntropin infusion) of three different doses of budesonide administered by means of the Turbuhaler to adult patients with mild asthma and compare the effects with those of an active control, oral prednisone 10 mg once daily, and placebo.

METHODS

Study design

This study was a double-blind, double-dummy, randomized, placebo-controlled, positive-controlled, parallel-group, multicenter design.

Patients initially underwent a 1-week screening period followed by a 1-week baseline period. During this time, medical histories were recorded, a physical examination was performed, blood samples were taken for clinical laboratory testing and determination of cortisol concentrations, lung function was measured, and the patient's ability to use the Turbuhaler and comply with the dosage regimen was assessed. Patients who successfully completed these stages were randomly allocated to receive double-blind treatment with either 800, 1600, or 3200 $\mu\text{g/day}$ budesonide (400, 800, or 1600 μg twice daily), placebo (lactose), or 10 mg oral prednisone once daily for 6 weeks starting at the first treatment visit. The last dose of each regimen was given in the morning the day before (i.e., 24 hours before the HPA axis function test). Each dose from the Turbuhaler consisted of two inhalations of study medication. To maintain blinding, patients assigned to the budesonide groups or the inhaled placebo group received placebo prednisone capsules; patients allocated to the oral prednisone group were issued inhaler devices containing placebo. Inhalers containing 100 doses of either budesonide 200, 400, or 800 μg or placebo and a bottle of 30 prednisone or placebo capsules were

dispensed to each patient at the start of the study and after 3 weeks of treatment.

Concurrent treatment with cromolyn sodium, nedocromil sodium, adrenaline, β -blockers, parenteral β -agonists, or combinations of expectorants or sedatives with bronchodilators was not permitted and was withdrawn at the screening visit (i.e., 1 week before the baseline period). Inhaled β -agonists other than albuterol sulfate were also not allowed.

Subjects

Adult patients diagnosed as having asthma were enrolled into the study at five centers in the United States. Patients 18 to 65 years old of either sex were eligible for inclusion if they had an FEV₁ of 65% or greater of the predicted value. In addition, the patients had to demonstrate the ability to use the Turbuhaler and be able to achieve an inspiratory flow rate of 50 L/min or greater through the device. Before participating in the study, all patients had to give their written informed consent and be willing and able to complete a daily diary card.

Patients were not included if, during 4 weeks before inclusion in the study, their asthma had caused hospitalization or if they had suffered a significant chest or upper respiratory tract infection. Patients were excluded from the study if they had a history of carcinoma, a history of multiple drug allergies or hypersensitivity to corticosteroids, or any other significant disease or major physical impairment. Also excluded were patients receiving other corticosteroids or who had received any form of corticosteroid therapy in the previous 6 months, patients who had received investigational drugs in the previous 4 weeks, or patients who would be starting immunotherapy. Other reasons for exclusion were significantly abnormal basal plasma cortisol concentrations ($< 5.1 \mu\text{g/dl}$ or $< 140 \text{ nmol/L}$), significantly abnormal postcosyntropin infusion plasma cortisol responses, or both. Female patients were excluded if they were pregnant or lactating. Female patients must have had a negative serum pregnancy test, and unless they were surgically sterile or postmenopausal, had to be using a medically acceptable contraceptive technique other than contraceptive methods involving estrogen or progesterone.

Clinical assessments

Clinical assessments were performed on the first day of treatment, 3 and 6 weeks after the start of treatment, and, if necessary because of clinical or laboratory adverse events, 8 weeks after the start of treatment.

Plasma cortisol concentrations and cosyntropin-stimulated cortisol secretion

At the beginning of the baseline period, patients attended the clinic for blood sampling to determine basal plasma cortisol concentration. These samples were taken between 6:30 and 8:30 am from an indwelling needle or cannula in one arm. A 6-hour infusion of cosyntropin (Cortrosyn; 0.25 mg dissolved in 500 ml 0.9% sodium chloride solution) was started after the initial blood sample was collected through a cannula or needle inserted into the patient's other arm. During the infusion period, the patient remained seated or recumbent. Blood samples were collected through the same needle or cannula as the preinfusion sample 2, 4, and 6 hours after starting the cosyntropin infusion. The needle or cannula was kept patent between blood samples with a diluted (10 U/ml) heparin solution. The sampling and infusion procedure was repeated at the end of the 6 weeks of double-blind treatment.

Each blood sample was placed in a heparinized tube and

TABLE I. Demographic characteristics

Characteristic	Placebo (n = 13)	Budesonide			Prednisone 10 mg once daily (n = 13)
		800 µg/day (n = 13)	1600 µg/day (n = 12)	3200 µg/day (n = 13)	
Sex					
M	11	9	11	8	10
F	2	4	1	5	3
Age (yrs)					
Mean	28.8	35.0	29.3	27.5	32.6
Range	18-43	21-57	18-56	18-38	22-52
Duration of asthma (yrs)					
Mean	21.5	18.1	18.0	14.0	18.6
Range	4.5-39.0	3.0-37.5	3.5-56.0	1.0-33.0	4.0-40.0
FEV ₁ (L)					
Mean	3.22	3.35	3.98	3.88	3.53
Range	2.64-3.99	1.84-4.58	2.59-6.19	2.68-8.40	2.60-4.55
PIF (L/min)					
Mean	88.6	87.1	84.8	89.2	84.9
Range	71.0-126.0	73.0-108.0	66.0-97.0	66.0-114.0	56.0-108.0
Basal plasma concentration (nmol/L)					
Mean	350	422	321	302	374
Range	232-513	193-905	146-590	138-524	163-568

PIF, Peak inspiratory flow.

centrifuged immediately at 1500g for 10 minutes. Plasma was removed and placed in a 10 ml polystyrene tube and mixed well. At least 2.5 ml of plasma was then transferred to a 5 ml polystyrene tube and stored at -20° C until analysis.

The determination of the concentration of cortisol in plasma was conducted at SmithKline Beecham Clinical Laboratories. The assay was based on liquid chromatography with ultraviolet detection and modified from Van den Berg et al.¹⁹ The lower limit of quantification for plasma cortisol concentration was 27.6 nmol/L.

Safety assessments

The primary method used to determine the occurrence of adverse events was by means of standard questions from the study investigator, inquiring about health problems or symptoms experienced by the patient since the last visit. Symptoms that were reported spontaneously by the patients were also recorded. Patients were instructed to record any adverse event on daily diary cards.

Routine hematology and blood chemistry and urine testing were performed at the end of the screening period, the end of the baseline period, and at the end of treatment. Serum pregnancy tests were carried out at screening and after treatment.

All patients underwent a full physical examination, and a record was made of vital signs at screening and after treatment; a 12-lead electrocardiogram was obtained during the screening period.

Patient compliance and withdrawal

Patient compliance with treatment was assessed by the use of daily diary cards and by recording the quantity of double-blind study medication used.

Patients were withdrawn from the study if they experienced intolerable adverse events, worsening asthmatic symptoms, or if exclusion criteria or concurrent disease developed. Patients

could be withdrawn from the study at the discretion of the investigator.

Ethical considerations

The protocol procedures and consent form were approved by the appropriate Institutional Review Board before initiation of the study. The study was performed in accordance with the principles stated in the Helsinki Declaration.

Data management and evaluation

The goal of the study was to obtain 10 evaluable patients per treatment group; thus a total sample size of 50 patients was planned. With this sample size, a difference in the primary effect variable, postcosyntropin plasma cortisol concentrations before and after 6 weeks of treatment, of 330 nmol/L (or 12 µg/dl) between two treatment groups could be detected with 80% power, assuming a standard deviation of 250 nmol/L (or 9 µg/dl) and a two-tailed significance level of 0.05.

The primary variable was the change from baseline to the end of 6 weeks of treatment in the stimulated plasma cortisol concentration measured after the 6-hour cosyntropin infusion. Treatment groups were compared with the use of a two-way analysis of variance (ANOVA), with treatment and center as main factors. The key comparisons were (1) to compare the prednisone and placebo groups when an effect was expected and (2) to assess the budesonide dose-response relation and estimate the dose of budesonide with an effect equivalent to 10 mg once daily prednisone (the latter comparison was performed with the use of a linear regression model).

Secondary variables were also assessed by ANOVA, including the change from baseline to end of treatment in the increase in plasma cortisol concentrations after 6 hours of cosyntropin infusion relative to the basal (before cosyntropin) values (Δ -cosyntropin plasma cortisol) and the change from baseline to end of treatment in basal plasma cortisol concentration.

The primary analysis was the per-protocol analysis on all

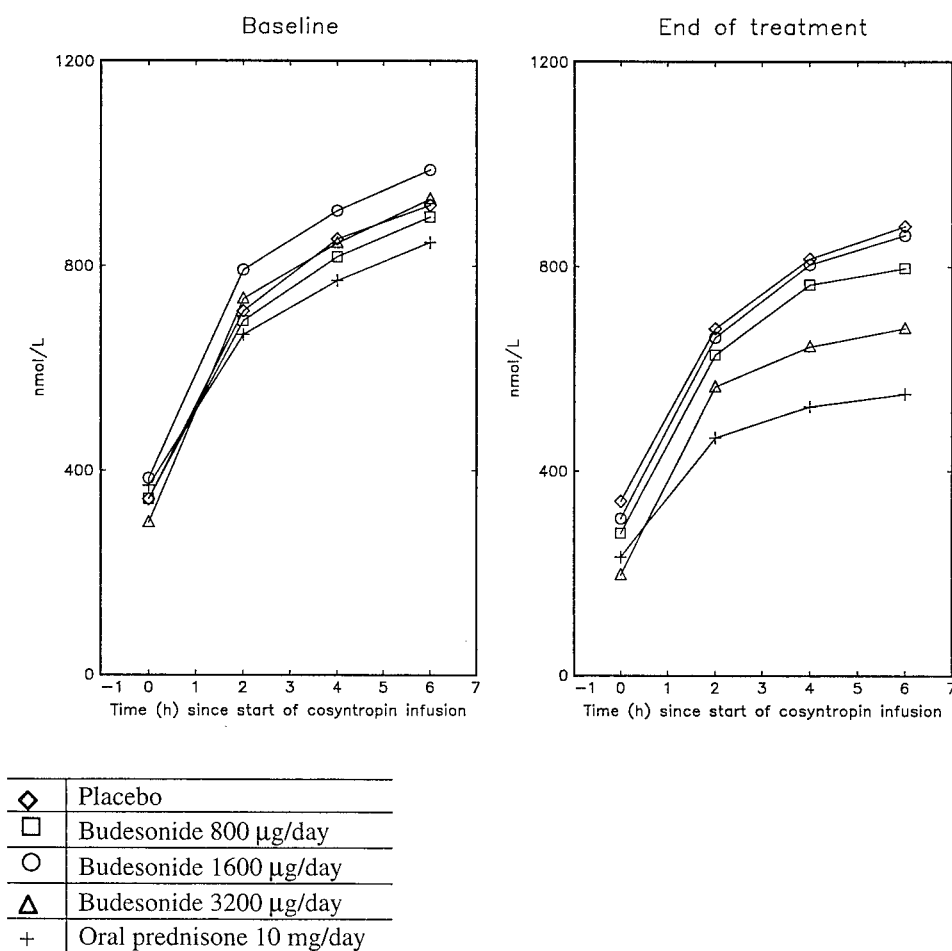


FIG. 1. Mean values of plasma cortisol concentration before and during continuous 6-hour infusion of cosyntropin at baseline and after 6 weeks of treatment with three different daily doses of inhaled budesonide or placebo or oral prednisone.

patients considered evaluable for this analysis. For urine cortisol concentration assessment, a per-protocol analysis was performed on the amount of cortisol secreted, and an all-patients-treated analysis was performed on the fraction of secreted urine cortisol/secreted urine creatinine. Data were analyzed with the GAUSS (Aptech Systems Inc.) version 3.0.

RESULTS

Patients

A total of 64 patients were randomized to the double-blind phase of this study. Of these, 13 patients received 800 µg/day budesonide, 12 patients received 1600 µg/day budesonide, 13 patients received 3200 µg/day budesonide, 13 patients received placebo, and 13 patients received 10 mg once daily prednisone.

The treatment groups were similar with respect to age, sex distribution, duration of asthma, lung function, basal plasma cortisol concentrations, and basal urine cortisol concentrations. The demographic characteristics are summarized in Table I.

Of the 64 patients who started the study medication, a

total of 58 patients completed 6 weeks of treatment. One patient each in the budesonide 800 and 1600 µg/day groups, the placebo group, and the prednisone groups was withdrawn because of poor compliance or failure to fulfill inclusion criteria. Two patients from the budesonide 3200 µg/day group discontinued the study, both because of adverse experiences. In addition, because of failure to fulfill the per-protocol analyses criteria, one patient each in the budesonide 800, 1600, and 3200 µg/day groups was excluded from assessments of plasma cortisol concentrations. Thus a total of 55 patients (11 from the budesonide 800 µg/day group, 10 each from the budesonide 1600 and 3200 µg/day groups, and 12 each from the placebo and prednisone groups) were evaluable for changes in cosyntropin-stimulated cortisol secretion and in basal plasma cortisol concentrations.

Cortisol during cosyntropin infusion

Mean plasma cortisol concentration before (0 hours) and during the cosyntropin infusion are shown in Fig. 1. Generally, at both assessments, plasma cortisol concen-

TABLE II. Mean plasma cortisol concentration (SEM) at the end of a 6-hour cosyntropin infusion at baseline and at the end of treatment, obtained from per-protocol ANOVA, together with mean changes between assessments

Treatment group	Mean postcosyntropin plasma cortisol (nmol/L)		Adjusted mean change (nmol/L)	Percentage change	Comparison vs placebo (<i>p</i> value)*	Comparison vs prednisone (<i>p</i> value)*
	Baseline	End of treatment				
Placebo	919 (33)	879 (66)	-48	-4.4	...	0.005
Budesonide 800 µg/day	988 (81)	862 (46)	-137	-12.7	NS	0.08
Budesonide 1600 µg/day	896 (46)	797 (47)	-90	-11.1	NS	0.03
Budesonide 3200 µg/day	931 (26)	679 (50)	-249	-27.1	0.03	NS
Prednisone 10 mg/day	846 (25)	551 (30)	-292	-34.9	0.005	...

*Probability values > 0.1 are denoted not significant (NS); values < 0.05 are considered statistically significant.

trations increased during cosyntropin infusion, approaching a plateau toward the end of the 6-hour infusion period.

The basal, as well as the cosyntropin-stimulated increase in plasma cortisol, concentration was reduced by corticosteroid treatment. Prednisone showed the greatest suppressive effect and budesonide showed a dose-related effect, as illustrated in Fig. 1.

Table II shows the results from the primary analysis. Mean percentage decrease in postcosyntropin plasma cortisol concentration at the end of treatment (visit 5) and baseline (visit 2) was approximately 4%, 13%, 11%, 27%, and 35% for the placebo group; the 800, 1600, and 3200 µg/day budesonide groups; and the prednisone group, respectively. Compared with placebo, only the decreases seen in the budesonide 3200 µg/day and prednisone 10 mg once daily groups were statistically significant (*p* = 0.03 and *p* = 0.005, respectively). Furthermore, the decrease in postcosyntropin plasma cortisol concentration in the 10 mg once daily prednisone group was significantly greater than that found in the budesonide 1600 µg/day group (*p* = 0.03) and approached statistical significance when compared with the budesonide 800 µg/day group (*p* = 0.08). No significant difference was shown in the decrease in plasma cortisol concentrations between the 10 mg prednisone and 3200 µg/day budesonide groups.

Individual values for plasma cortisol concentrations at the end of cosyntropin infusion are presented in Fig. 2. At the end of treatment, all patients who received 10 mg once daily prednisone and all except one patient who received budesonide 3200 µg/day showed a decreased adrenal response to the 6-hour cosyntropin infusion. In the remaining treatment groups, the decreases were generally less marked or absent except for two aberrant results, one patient who received placebo and another who received budesonide 800 µg/day. Although the patient who received placebo showed a normal adrenal response at baseline (plasma cortisol concentration was 513 and 814 nmol/L before and after cosyntropin infusion, respectively), at the end of treatment the adrenal response was virtually absent (plasma cortisol concentration was 185 and 201 nmol/L before and after cosyntropin

infusion, respectively). At baseline, one patient in the 800 µg/day budesonide group had unusually high cortisol concentrations both before and after cosyntropin infusion (905 and 1730 nmol/L, respectively); however, both basal and postcosyntropin plasma cortisol concentrations were normalized after 6 weeks of treatment (406 and 745 nmol/L, respectively).

There was no consistent dose-response decrease in postcosyntropin plasma cortisol concentrations, although treatment with 800 and 1600 µg/day budesonide resulted in a smaller decrease in plasma cortisol concentration in comparison with 3200 µg/day budesonide. However, when the two aberrant results mentioned above were excluded from the ANOVA, the change in plasma cortisol concentrations between the 800 µg/day budesonide group and the prednisone group was significant (*p* < 0.001), and there was a consistent dose-response relation among the three doses of budesonide in suppression of postcosyntropin cortisol secretion. Hence, bioequivalent doses of prednisone and budesonide could be estimated. The result from that analysis was that 10 mg prednisone once daily corresponded to a total daily dose of 5 mg (95% confidence interval: 1.2 to 34.8 mg/day) of inhaled budesonide with regard to its effects on adrenal stimulation.

The difference between baseline and the end of treatment in the change from post- and precosyntropin infusion concentrations of plasma cortisol (Δ -cosyntropin plasma cortisol) was also investigated. Although decreases in Δ -cosyntropin plasma cortisol were observed in all five groups at the end of treatment, none of the changes in the active treatment groups were significantly different from those in the placebo group (Fig. 3).

Basal cortisol

Basal plasma cortisol concentrations (i.e., those taken before the start of cosyntropin infusion) at baseline and at the end of treatment are summarized in Fig. 4. The mean values decreased by approximately 19%, 19%, 34%, and 37% for the budesonide 800, 1600, and 3200 µg/day groups and the prednisone-treated patients, respectively. In the placebo group, the reduction was 1%. Only the reduction in basal

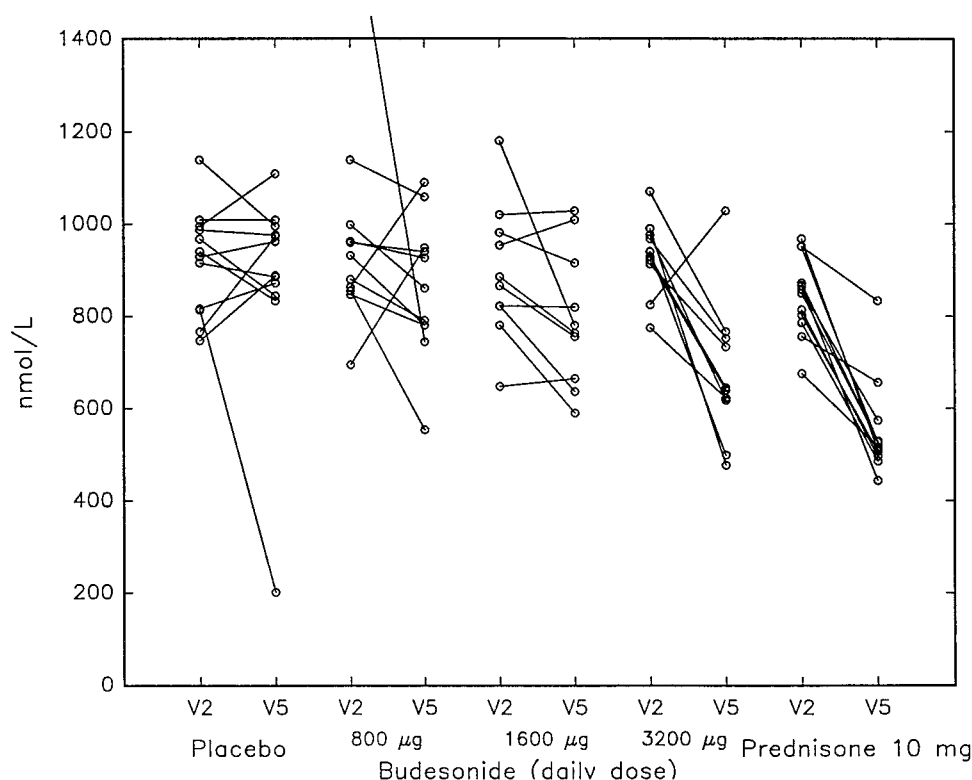


FIG. 2. Individual plasma cortisol concentrations after 6-hour cosyntropin infusion at baseline (V2) and after 6 weeks of treatment (V5) with three different daily doses of inhaled budesonide or placebo or oral prednisone.

plasma cortisol concentration in the 10 mg prednisone group compared with the placebo group was significantly different ($p = 0.025$).

Safety assessments

The majority of patients in all treatment groups experienced adverse events during double-blind treatment, and the overall incidence was similar in all groups. Adverse events believed by the investigators to be possibly or probably related to study medication were recorded for four patients in the 800 µg/day budesonide group, two in the 1600 µg/day group, six in the 3200 µg/day group, two in the placebo group, and one in the prednisone group. Only two patients, both from the 3200 µg/day budesonide group, discontinued the study because of adverse events possibly related to study medication. In one patient these adverse events were light-headedness, stomach pain, coughing, sore throat, and nasal congestion; in the other, menorrhagia. None of the adverse events were considered to be serious.

DISCUSSION

Budesonide, inhaled by means of the Turbuhaler, is efficacious for the treatment of chronic persistent asthma at a dose of 200 to 1600 µg/day. Within this dose range, Busse²⁰ was able to show a dose response in antiasthma effect in patients with moderate-to-severe inhaled steroid-dependent asthma. In this study budes-

onide doses in the upper range of clinically recommended doses were selected (800 and 1600 µg/day). Also, a dose twice the proposed maximum recommended dose (3200 µg/day) was given to one group of patients. Placebo and oral prednisone groups were included for comparison. The dose of oral prednisone chosen (10 mg/day) has a relatively insignificant antiasthma effect²¹ and has been claimed by some to be without clinically important adverse effects.²² Corticosteroid-related suppression of the HPA axis was quantified by measurement of the response to exogenous adrenal stimulation (6-hour infusion of cosyntropin) before and after 6 weeks' treatment with the study medication.

The most commonly used technique of screening HPA axis function is the measurement of the concentration of cortisol in a single morning sample of plasma. Although this method gives an indication of the exogenous effects of corticosteroids, it is limited by its variability. Single plasma cortisol concentrations are an indirect measurement of adrenal function, relevant only to the time of sampling, and give little or no information regarding the HPA axis function before or after sampling. Repeated plasma sampling and 24-hour urinary cortisol excretion may be better indirect measures of HPA axis function.²³ With the use of these sensitive methods, 1600 µg/day budesonide, inhaled by means of the Turbuhaler, has a statistically significant effect on plasma cortisol area under the curve (0 to 24 hours).¹⁰

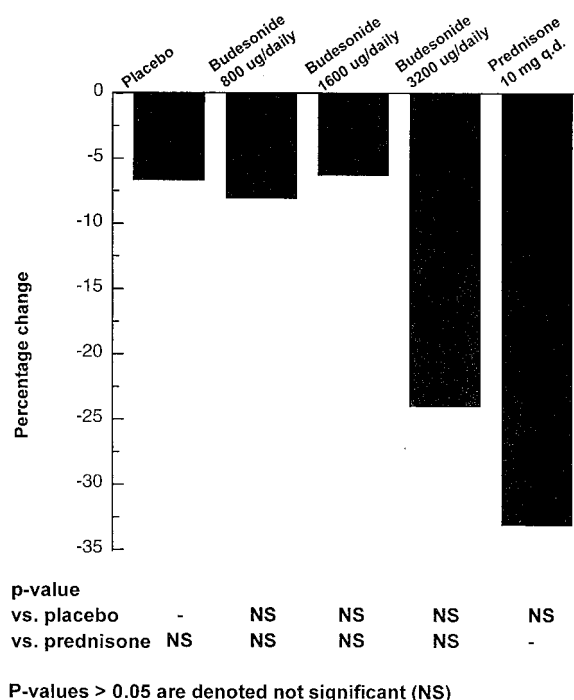


FIG. 3. Percentage change from baseline to end of treatment in response to cosyntropin infusion (Δ -cosyntropin plasma cortisol).

A more direct measurement of HPA axis function is the cosyntropin-stimulated increase in cortisol secretion. This frequently used short-term analysis (bolus injection of cosyntropin) has been used previously to evaluate the effect of budesonide. In one study, 1600 μ g/day budesonide, inhaled by means of a pMDI for 6 weeks, had no effect on the HPA axis.²⁴ In studies in which patients changed from oral corticosteroids to inhaled budesonide, the adrenal response was improved.^{25, 26}

In this study a 6-hour infusion of cosyntropin was used. This method has been reported to be more reliable than the bolus injection.¹³

Inhaled budesonide at 800 or 1600 μ g/day did not produce a statistically significant reduction in the cosyntropin-stimulated adrenal secretion of cortisol after 6 weeks of treatment compared with placebo. Budesonide (3200 μ g/day), which is twice the highest recommended dose for clinical use in asthma, caused significant suppression of adrenal cortisol production. This reduction in cortisol production was of a magnitude similar to that observed with 10 mg prednisone once daily. Almost the same suppression of cortisol secretion by 10 mg prednisone once daily was observed in a study of similar design by Feiss et al.¹⁴ In addition, fluticasone propionate delivery by pMDI,¹⁵ but not triamcinolone acetonide¹⁶ or flunisolide delivered by pMDI,¹⁷ caused abnormal cortisol production in asthmatic patients receiving 1000 μ g/day when assessed by 6-hour cosyntropin infusion in placebo-controlled, parallel-group studies with 28 days of treatment. This is in agreement with a study comparing plasma cortisol suppression

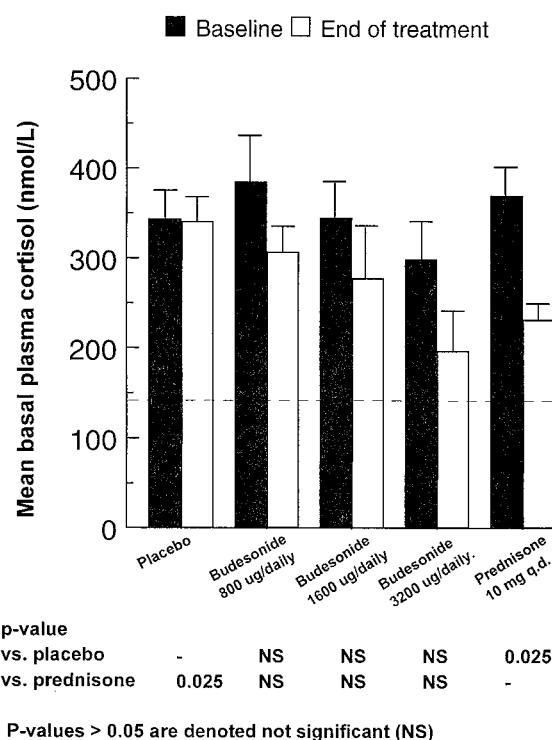


FIG. 4. Baseline and end of treatment basal (before cosyntropin infusion) plasma cortisol concentration. Arithmetic means and standard error of means are given. The lower limit for significantly abnormal basal plasma cortisol concentration (140 nmol/L) is indicated (dashed line).

among beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, and triamcinolone acetonide, in which only fluticasone propionate was found to produce significant suppression of 24-hour plasma cortisol compared with the other inhaled corticosteroids after a single dose of 1000 μ g and after 3.5 days of dosing of 1000 μ g twice daily.²⁷

In a study by Toogood et al.²¹ in 1989, budesonide had an antiasthmatic potency that was approximately 58 times greater than that found for prednisone, whereas the systemic glucocorticoid potency (as determined by a combination of blood eosinophil count and morning serum cortisol) only differed ninefold. This indicates that budesonide has a favorable therapeutic ratio (i.e., a desirable topical antiasthmatic effect vs an unwanted systemic effect) compared with prednisone. The systemic potency ratio was only twofold in the current study, which may be explained by differences in the methods used and the patients selected.

A dose-response relation in the suppression of plasma cortisol secretion was shown among the three doses of budesonide when aberrant values for two patients, one in the placebo group and the other in the 800 μ g/day budesonide group, were excluded. This confirms that the methods used in this study for the assessment of cortisol changes were sufficiently sensitive to detect relevant differences among the treatment groups. The fact that

only the postcosyntropin test, and not basal cortisol or the Δ -cosyntropin plasma cortisol test, could statistically discriminate between any budesonide dose and placebo as well as between budesonide and prednisone. This indicates that the postcosyntropin test was accurately selected as the primary and most sensitive end point of those used in this study.

No serious adverse events occurred during this study, and all doses of budesonide were generally well tolerated. There were no clinically important differences in adverse events between patients who received all three doses of budesonide compared with those who received placebo.

In conclusion, in this study budesonide inhaled by means of the Turbuhaler at doses recommended for clinical use (800 or 1600 μ g/day) did not produce any statistically significant suppression of the HPA axis compared with placebo. At twice the highest recommended dose for clinical use in asthma (3200 μ g/day), budesonide produced a suppression of adrenal cortisol production of a magnitude similar to that observed with 10 mg of prednisone. The study also indicates that the 6-hour cosyntropin infusion test is an informative test of HPA axis function, with a sensitivity that appears similar to that of other methods, such as plasma cortisol area under the curve (0 to 24 hours).

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