

Effects of High-Dose Inhaled Corticosteroids on Plasma Cortisol Concentrations in Healthy Adults

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Background: Recent studies suggest that inhaled corticosteroids may differ significantly in their systemic effects.

Objective: To compare the systemic effects, as measured by plasma cortisol suppression, of inhaled beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, and triamcinolone acetonide at doses of approximately 1000 µg twice daily.

Methods: Sixty healthy adult male volunteers participated in this randomized, open-label, parallel-design study. Twenty-four-hour plasma cortisol determinations (cortisol-AUC₂₄) were measured after a single dose of placebo medication and after a single dose and 7 consecutive doses of active medication.

Results: After a single dose, all inhaled corticosteroid preparations caused statistically significant mean reductions in cortisol-AUC₂₄ compared with placebo as follows: flunisolide, 7% ($P = .02$); budesonide, 16% ($P = .001$);

beclomethasone, 18% ($P = .003$); triamcinolone, 19% ($P = .001$); and fluticasone, 35% ($P < .001$). After multiple doses, flunisolide was not significantly different from placebo (5%; $P = .24$), while budesonide (18%; $P = .002$), triamcinolone (25%; $P < .001$), beclomethasone (28%; $P < .001$), and fluticasone (79%; $P < .001$) all resulted in statistically significant suppression of cortisol-AUC₂₄. After both single and multiple doses, beclomethasone, budesonide, flunisolide, and triamcinolone were not statistically different from each other, while fluticasone was significantly ($P < .001$) more suppressive than the other 4 medications.

Conclusions: These results indicate that there are differences in the systemic effects of inhaled corticosteroids when used in high doses and emphasize the importance of using the minimum dose of inhaled corticosteroids required to maintain control of asthma symptoms.

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INHALED corticosteroid (ICS) preparations have become widely accepted as first-line treatment for persistent symptoms of bronchial asthma.¹ As physicians have increasingly prescribed corticosteroid aerosols in higher doses, there have also been growing concerns regarding possible systemic effects. Short-term clinical studies performed in healthy volunteers and subjects with asthma have demonstrated that high doses of ICS may affect hypothalamic-pituitary-adrenal (HPA) axis function,² bone density,³ bone metabolism,⁴ collagen synthesis in the skin,⁵ and skin thickness.⁶ In clinical trials of ICS agents, single morning plasma cortisol determinations are often the principal test used to assess the presence of systemic effects.² While single morning samples frequently yield normal results across a wide range of ICS doses, measurement of cortisol production throughout an entire day has been

found to be much more sensitive in detecting systemic effects and may demonstrate cortisol suppression after brief periods of treatment with corticosteroids.⁷⁻¹⁰

Currently, 5 corticosteroid aerosols are available in the United States: beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, and triamcinolone acetonide. While all these medications have been shown to be effective in the treatment of asthma,¹¹ there is evidence that beclomethasone, budesonide, and fluticasone differ significantly in their systemic effects.⁸⁻¹⁰ However, few data exist regarding either flunisolide or triamcinolone, and, to our knowledge, there have been no direct comparisons of all 5 of these medications in a single study. Therefore, the purpose of the present investigation was to compare the relative systemic effects of the available ICS preparations, given in high doses, using a very sensitive and precise

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SUBJECTS AND METHODS

SUBJECTS

Sixty healthy adult male volunteers (age range, 18-33 years; mean \pm SD age, 22.5 \pm 3.1 years) took part in the study. All had a body weight within 15% of normal body weight relative to height and frame size. One week before beginning the study, all subjects underwent a complete history and physical examination, blood chemistry panel, complete blood cell count, electrocardiography, and spirometry. None of the subjects had a history or current evidence of asthma or allergic rhinitis, and none had used systemic or topical corticosteroids during the past year. The chemistry and hematologic values and the electrocardiographic and spirometric findings were normal in all subjects. Written informed consent was obtained from all participants, and approval from an independent medical ethics committee was obtained before the start of the study.

PROTOCOL

The study used a randomized, parallel-group, open-label design and a single dose of placebo. Several hours before beginning the study, the subjects were admitted to a clinical research facility (PharmaBio Research, Zuidlaren, the Netherlands), where they remained until the completion of the 7-day study. They were placed on a standardized diet and schedule of activity and refrained from exercise.

Day 1 served as a placebo control period for all subjects, with a single dose of placebo inhalant administered at 10 PM. On day 2 at 10 PM, the subjects were randomized to 1 of 5 treatment groups and received a dose of beclomethasone, budesonide, flunisolide, fluticasone, or triamcinolone (**Table**). On days 3 to 6, they received the same dose of their study medication twice daily at 10 PM and 10 AM. Placebo and all study medications were administered with

metered-dose inhalers. Triamcinolone was delivered using its built-in tube extender, while the other 4 medications were given without spacer devices. Two hours before dosing, all participants were instructed in the use of their oral inhalation device using the closed-mouth technique as described in the product inserts. Before each dose, or puff, was inhaled, the canister was primed and shaken, and the puffs were inhaled at intervals of 30 seconds. After each puff, the subjects held their breath for 10 seconds and did not rinse their mouths after completion of the inhalation. Blood was sampled for plasma cortisol levels via an indwelling catheter at 10 PM (immediately prior to drug dosing) and at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hours after dosing on days 1, 2, and 6. The analysis of cortisol from serial plasma samples (approximately 3 mL) was accomplished by a 3-phase assay process using liquid chromatography/mass spectrometry/mass spectrometry (Finigan TSQ 7000 mass spectrometer; Finigan Inc, San Jose, Calif). The level of detection for cortisol was 4.1 nmol/L (1.5 ng/mL), and the concentration range for the standard curve ranged from 4.1 to 551.8 nmol/L (1.5-200 ng/mL). The coefficient of variation for the cortisol assay ranged between 7% and 13%.

STATISTICAL ANALYSIS

The 24-hour plasma cortisol production was calculated as area under the cortisol concentration-time curve (cortisol-AUC₂₄) using the trapezoidal rule. Cortisol-AUC₂₄ was compared within treatment groups using the *t* test for the following parameters: (1) after a single dose of placebo (day 1) vs single (day 2) and multiple (day 6) doses of active medication, and (2) after single vs multiple doses of active medication. The mean percentage of suppression of cortisol-AUC₂₄ was compared between the 5 active treatment groups at days 2 and 6 by 1-way analysis of variance, making corrections for multiple comparisons using the Tukey test. A probability level of *P* < .05 (2-tailed) was considered to be significant for all tests.

indicator of HPA axis suppression under highly standardized conditions.

RESULTS

Cortisol-AUC₂₄ values were comparable after the inhalation of placebo (day 1) in each of the 5 treatment groups (**Figure 1**). On day 2, after a single dose of active medication, the compounds ranged widely in their suppression of 24-hour plasma cortisol levels. All 5 medications caused statistically significant suppression of the cortisol-AUC₂₄ as follows (from the least to the most suppressive): flunisolide, 7% (*P* = .02); budesonide, 16% (*P* = .001); beclomethasone, 18% (*P* = .003); triamcinolone, 19% (*P* = .001); and fluticasone, 35% (*P* < .001) (**Figure 2**). On day 6, after 7 consecutive doses of medication, flunisolide caused no significant suppression of cortisol-AUC₂₄ (5%), while budesonide (18%; *P* = .002), triamcinolone (25%; *P* < .001), beclomethasone (28%; *P* < .001), and fluticasone (79%; *P* < .001) all resulted in statistically significant suppression (Figure 2). When the suppressive effect of single vs multiple doses of ICS within each treatment group were compared, there were

no significant differences seen with beclomethasone, budesonide, flunisolide, and triamcinolone. Fluticasone, however, caused significantly more suppression after multiple doses than after a single dose (*P* < .001). While beclomethasone, budesonide, flunisolide, and triamcinolone did not vary statistically between each other after either single or multiple doses, fluticasone was significantly (*P* < .001) more suppressive than all the other compounds at both time points.

COMMENT

In the present study, we investigated the systemic effects of inhaled beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, and triamcinolone acetate at doses of approximately 1000 μ g twice daily under both single-dose and steady-state conditions. After a single dose of each of the compounds, flunisolide exhibited the smallest degree of suppression, followed by budesonide, beclomethasone, triamcinolone, and fluticasone. After multiple doses, beclomethasone, budesonide, flunisolide, and triamcinolone caused cortisol suppression similar to that seen

Doses of Inhaled Corticosteroids Used in Study

Compound	Micrograms per Puff	No. of Puffs per Dose	Dose, µg/d
Beclomethasone dipropionate	220	4	880
Budesonide	180	5	900
Flunisolide	250	4	1000
Fluticasone propionate	220	4	880
Triamcinolone acetonide	100	10	1000

after a single dose, while the suppression caused by fluticasone increased significantly. There were no statistical differences between beclomethasone, budesonide, flunisolide, and triamcinolone ($P > .05$) after either single or multiple doses, while fluticasone was notably more suppressive than the other 4 drugs ($P < .001$).

These data are in agreement with the findings of other studies that have examined the effects of beclomethasone, budesonide, and fluticasone on serial plasma cortisol concentrations in healthy volunteers.⁷⁻¹⁰ Brown et al⁷ compared the effects of a single, 1000-µg dose of beclomethasone dipropionate and budesonide on serial plasma cortisol levels (measured between 4 and 6 hours after dosing) and noted similar levels of suppression with both inhalants. Grahnen et al⁸ studied the effects of budesonide and fluticasone in serial cortisol samples collected over a 20-hour period. The cortisol suppression caused by single 250, 500, and 1000-µg doses of fluticasone propionate was 8%, 19%, and 28%, respectively, while 800 µg of budesonide caused 16% suppression. Multiple 1000-µg doses of fluticasone propionate given twice daily for 3.5 days resulted in 65% suppression compared with placebo; budesonide was not studied after multiple doses. Lonnebo et al⁹ compared the effects of budesonide and fluticasone on serial serum cortisol concentrations. A single 800-µg dose of budesonide induced a 26% reduction in cortisol-AUC₂₀, while a single 1000-µg dose of fluticasone propionate resulted in 25% suppression. After 3.5 days of twice-daily dosing, however, suppression caused by budesonide and fluticasone had increased to 34% and 65%, respectively. Boorsma et al¹⁰ compared the effects of 3 different doses of budesonide and fluticasone (taken twice daily for 4 days) on 24-hour serum cortisol concentrations.¹⁰ Budesonide at doses of 200, 400, and 1000 µg caused 1%, 3%, and 27% suppression of cortisol-AUC₂₄, while fluticasone propionate at doses of 200, 375, and 1000 µg induced 21%, 39%, and 84% suppression. The relative systemic potency of fluticasone was calculated as 3.7-fold higher than that of budesonide. In the studies by Grahnen et al⁸ and Lonnebo et al,⁹ the 2 drugs were administered by different delivery systems (budesonide by Turbohaler [Astra Pharmaceuticals, Sodertalje, Sweden] and fluticasone by Diskhaler [Allen and Hanburys, Middlesex, England]), making accurate comparisons difficult. Boorsma et al,¹⁰ however, administered both medications by metered-dose inhalers, allowing for comparable drug deposition into the lower airways.

Together with the results from our current trial, the above study findings suggest that when administered in

approximate microgram-equivalent doses, beclomethasone dipropionate, budesonide, flunisolide and triamcinolone acetonide cause statistically similar levels of plasma cortisol suppression, while fluticasone propionate results in significantly more suppression than the other compounds. Although the results of our study and others allow us to compare systemic effects of the medications at a dose of 1000 µg twice daily, calculation of the systemic potency ratios for the 5 inhalants requires that dose-response curves be determined for all drugs in the same study.

When comparing the cortisol suppression induced by single vs multiple doses of ICS, it is important to acknowledge that corticosteroid inhalants are administered on a regular rather than intermittent basis. Therefore, results derived at steady-state conditions are far more relevant to the actual use of these medications. Single-dose data are most helpful in determining whether accumulation has occurred with a particular drug, as evidenced by the significantly higher suppression of cortisol production after multiple doses compared with single-dose administration.

This investigation and the other 4 studies cited above were conducted with normal subjects rather than with patients with asthma. Since the primary goal of these studies is to investigate cortisol suppression as a marker for systemic corticosteroid effects, accurate comparison of these medications is predicated on comparable levels of deposition into the lower airways. Had the above trials used patients with asthma instead of normal subjects, differences in pulmonary function between the treatment groups may have resulted in significant differences in drug deposition into the lungs, making comparisons between the drugs difficult.

Clinical efficacy trials often rely on single morning plasma cortisol samples to evaluate systemic effects. However, the effects of exogenous corticosteroids on the HPA axis may be limited to subtle shifts in the diurnal release of cortisol, which may not be detected by sampling at a single time point.¹² Additionally, single cortisol measurements have significant intersubject and intrasubject variability, which may also make it difficult to demonstrate changes between treatment groups.¹³ Variability is further increased in outpatient studies, in which the timing and events preceding (stress and activity levels) blood sampling are not stringently controlled. Assessment of cortisol suppression throughout a longer period (8-24 hours) using serial blood samples or urine collections is a far more sensitive method, even at low doses of ICS.¹²

Systemic effects of corticosteroids are determined by the pharmacokinetic (particularly systemic availability and serum half-life) and pharmacodynamic (biologic activity) properties of a particular compound.¹⁴ With respect to systemic availability, approximately 80% to 85% of an inhaled dose of ICS delivered by a metered-dose device is swallowed and available for oral absorption, and 15% to 20% of the dose is delivered into the lungs.¹⁵ Fluticasone has extremely low oral availability (<1%) compared with triamcinolone, flunisolide, beclomethasone, and budesonide (approximately 23%, 21%, 20%, and 11%, respectively¹⁶). However, all gluco-

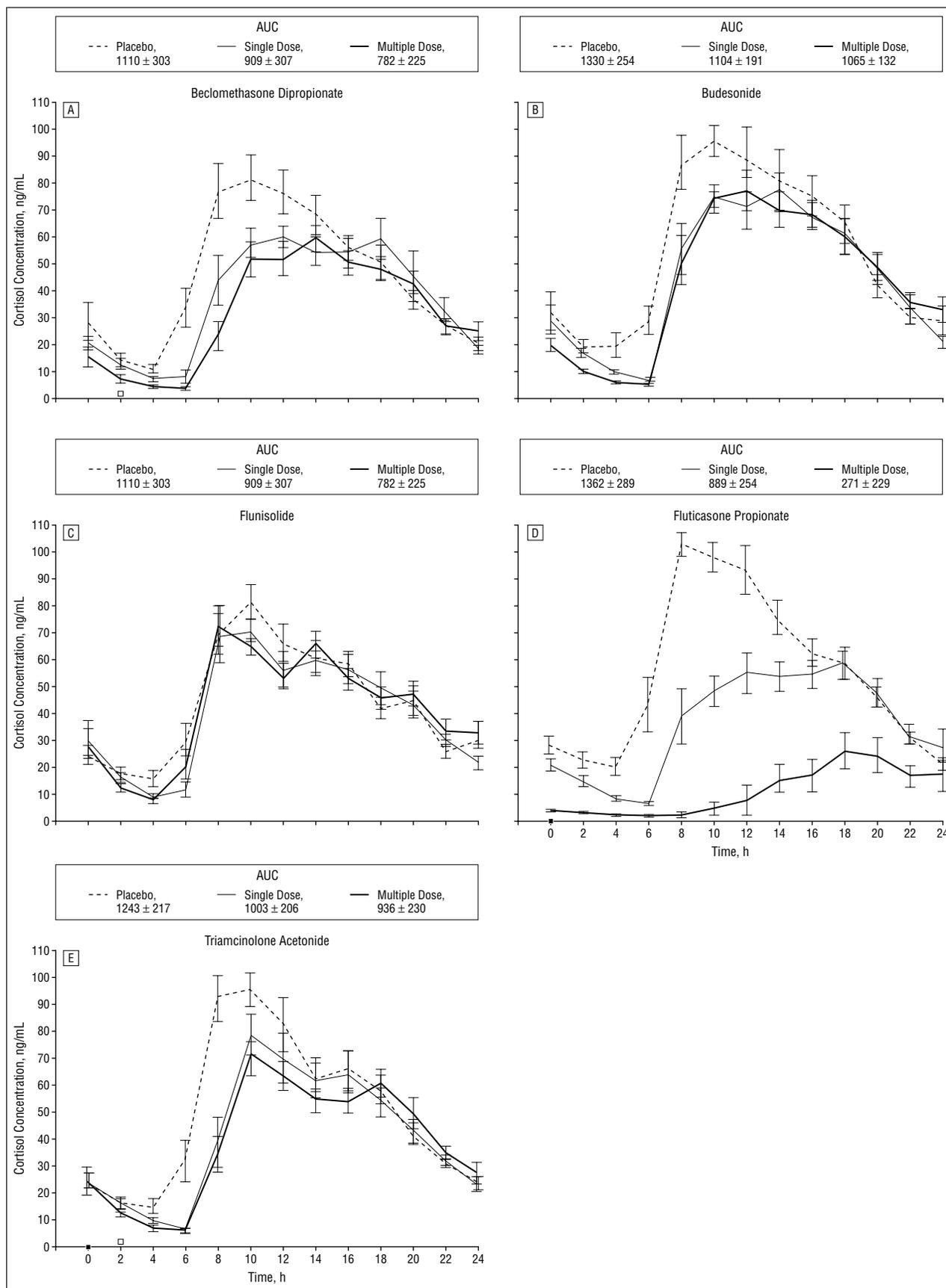


Figure 1. Plasma cortisol concentrations of the 5 study medications (A-E) measured every 2 hours for 24 hours after a single dose of placebo, a single dose of inhaled corticosteroid, and multiple doses of inhaled corticosteroid. AUC indicates area under the cortisol concentration–time curve, the values of which are expressed as mean ± SD. The error bars indicate SEM.

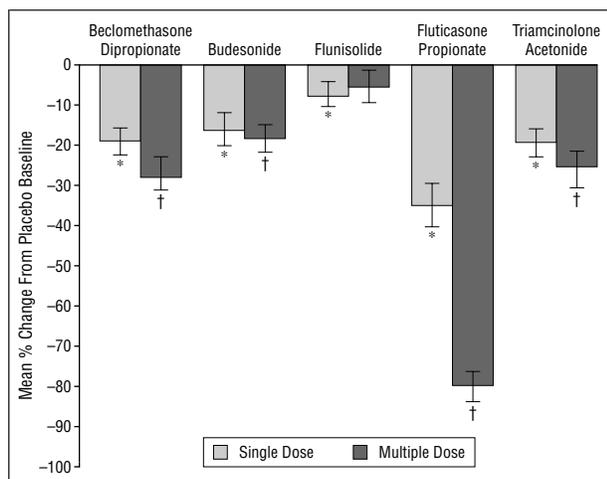


Figure 2. Mean percentage of change (with SEM indicated by error bars) from placebo baseline in area under the cortisol concentration-time curve at 24 hours after single and multiple doses of inhaled corticosteroid. Asterisks indicate $P < .01$; daggers, $P < .001$.

corticoid compounds delivered by the inhaled route are equally and completely absorbed from the lung into the systemic circulation, which contributes significantly to systemic bioavailability. The 5 drugs studied in the current trial may also be distinguished by their serum half-lives, with the $t_{1/2}$ for fluticasone, budesonide, flunisolide, and triamcinolone calculated as 7.8, 2.8, 1.6, and 1.5 hours, respectively^{16,17}; accurate information is not currently available for beclomethasone. As a consequence of this significantly longer half-life, when fluticasone is dosed twice daily it accumulates in the human body to a greater degree than the other compounds. This accumulation is most likely responsible for the higher levels of cortisol suppression seen after multiple doses of fluticasone compared with a single dose. With respect to the pharmacodynamic profile of the 5 medications, both in vitro and in vivo studies have demonstrated that the biologic activity of fluticasone is higher than that of the other 4 compounds studied in our trial.^{18,19} These differences appear to be principally determined by the binding affinities of these compounds for the glucocorticoid receptor.²⁰ In summarizing the effects of these multiple pharmacological characteristics, a compound that has more systemic availability, a longer half-life, and higher receptor-binding affinity for the glucocorticoid receptor would be expected to exert greater systemic effects.

The potential for an ICS to cause greater systemic effects must be considered in the context of comparative clinical efficacy. Fluticasone has been evaluated in multiple comparative trials with beclomethasone dipropionate and budesonide and has been demonstrated to be as clinically effective as these medications given at approximately twice the dose.²¹⁻²³ However, in one trial that used high doses of both fluticasone propionate and beclomethasone dipropionate (1500 and 1600 $\mu\text{g}/\text{d}$, respectively), there were no differences in control of asthma symptoms or measures of pulmonary function.²⁴ These data therefore suggest that at very high doses, ICS agents may be comparable in effi-

cacy but differ significantly in their potentials for systemic effects.

Suppression of cortisol production, particularly as assessed by integrated measurements over time, appears to be a very sensitive marker for the systemic effects of exogenous corticosteroids. An important issue for consideration is whether these changes in cortisol concentrations correlate with serious, long-term adverse effects, such as osteoporosis in adults and growth retardation in children. In a cross-sectional analysis study, patients with asthma who were using relatively high doses of beclomethasone dipropionate and budesonide (mean dose, 1323 $\mu\text{g}/\text{d}$; mean duration, 29 months) demonstrated significantly lower bone density than a group of patients with asthma who were treated without inhaled or oral corticosteroids.³ Both morning cortisol levels and increases in cortisol levels after stimulation with corticotropin were lower in patients who were treated with ICS preparations, and these reductions correlated significantly with loss of bone density. From these preliminary observations, gross changes in HPA axis function as measured by morning cortisol concentrations appear to be associated with loss of bone density and reduction in growth in patients using moderate to high doses of ICS. Prospective investigations relating integrated plasma or urine cortisol concentrations to bone density and growth are needed to better define the relevance of the changes seen in our present study.

The results of this study describe the systemic effects of high doses of 5 corticosteroid inhalants used to treat asthma. These data reinforce the importance of using these medications in the lowest dose required to maintain control of asthma symptoms. The results also suggest that these medications, when used in high doses, are not interchangeable with respect to systemic effects. Well-designed future trials that characterize the comparative efficacies and systemic effects of these agents across a wide range of doses will be vital to the clinical care of patients with asthma.

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