

Clinical relevance of inhaled corticosteroids and HPA axis suppression

Robert G. Dluhy, MD *Boston, Mass.*

Although hypothalamic-pituitary-adrenal (HPA) axis suppression has traditionally been viewed as an adverse event after long-term administration of corticosteroids, this effect can also be used to compare the potency of different inhaled corticosteroids. However, various factors such as the dose, frequency of administration, treatment duration, study population (patients with asthma versus normal volunteers), and prior systemic steroid therapy influence adrenal suppression with inhaled corticosteroids. The different adrenal function tests available and the results produced with these tests also must be considered along with the clinical relevance of such results. Whereas low doses of inhaled corticosteroids are likely to cause minimal or no HPA axis suppression, long-term high-dose inhaled corticosteroid use may result in significant suppression by effectively replacing endogenous steroid production. The risk of acute adrenal insufficiency in patients taking low/medium-dose inhaled corticosteroids is minimal, but patients receiving long-term high-dose treatment may require supplementary systemic steroids during stress challenges, especially if they have previously received long-term systemic steroid treatment. (*J Allergy Clin Immunol* 1998;101:S447-50.)

Key words: *Inhaled corticosteroids, hypothalamic-pituitary-adrenal axis suppression, adrenal function tests*

Many studies that have reported suppression of the hypothalamic-pituitary-adrenal axis after use of inhaled corticosteroids have emphasized that this effect reflects a toxicity of these compounds. However, HPA axis suppression can also be viewed as a sensitive marker for the systemic bioavailability of inhaled corticosteroids from all sources, that is, the amount of a dose that is absorbed from the lung plus the amount that is swallowed and absorbed from the gut. Newer inhaled corticosteroids, primarily budesonide and fluticasone propionate, have reduced oral bioavailability and potentially lower systemic bioavailability because of extensive first-pass hepatic metabolism.¹ Other factors also influencing systemic bioavailability are highlighted in Table I. HPA axis suppression can be used to compare the systemic activity of different doses of different inhaled corticosteroids (so-called biologically equivalent dosing). Thus HPA axis suppression can be used to assess clinically the biologic potency of a compound, permitting microgram-per-microgram comparisons between the various inhaled corticosteroids. For example, in vitro and clinical HPA axis suppression studies indicate that BUD is

Abbreviations used

ACTH:	Adrenocorticotrophic hormone
AUC:	Area under the curve
BDP:	Beclomethasone dipropionate
BUD:	Budesonide
FP:	Fluticasone propionate
HPA:	Hypothalamic-pituitary-adrenal

about half as potent as FP (400 µg of BUD is biologically equivalent to 200 µg of FP).¹

It is likely that the HPA axis is the most sensitive index of glucocorticoid activity. However, the possibility remains that tissue sensitivities to glucocorticoids may differ, although in contrast with other hormones such as estrogens, there is a single family of glucocorticoid receptors.

A number of factors influence adrenal suppression with inhaled corticosteroids (Table II). The compound, dose, frequency of administration, and timing of dose each play a role in subsequent actions on the HPA axis. Another key variable is duration of treatment, while a confounding factor in many studies is prior long-term systemic steroid use. The study population is also important; healthy volunteers will absorb more of an inhaled steroid dose into their lungs compared with patients with asthma because of different airway diameters. Thus at comparable doses of an inhaled corticosteroid, more systemic bioavailability from the lungs would be expected in studies in healthy volunteers because of better delivery of the dose to the pulmonary parenchyma. Once delivered to the lungs, there is obligate absorption into the systemic circulation for all inhaled corticosteroids.

It is also known that there is significant interindividual variability of side effects in different populations taking a dose of glucocorticoid. However, it is not clear whether this variability in side effects, including HPA axis suppression, reflects pharmacokinetic differences (e.g., absorption and clearance) or genetic differences (e.g., receptor affinity).

TESTS OF ADRENAL FUNCTION

When assessing HPA axis suppression, it is important to understand the various tests of adrenal function that are available as well as the implications of the results of each test. Adrenal function tests can either assess basal secretory functions (morning cortisol, 24-hour cortisol profiling, or 24-hour urinary free cortisol) or involve stimulation testing (e.g., short [60-minute] or long [6- to

From Brigham and Womens Hospital, Boston, Mass.

Reprint requests: Robert G. Dluhy, MD, Brigham and Womens Hospital, 221 Longwood Ave., Boston, MA 02115.

Copyright © 1998 by Mosby, Inc.

0091-6749/98 \$5.00 + 0 1/0/86610

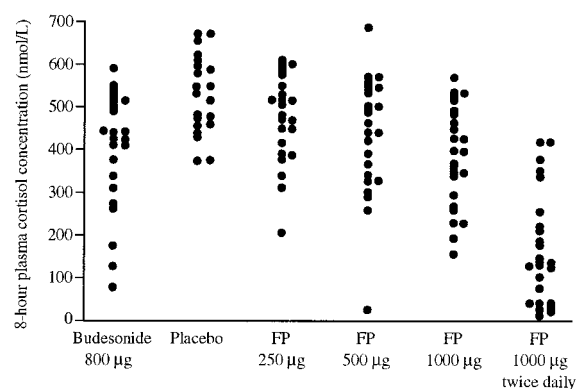


FIG. 1. Effect of budesonide (800 µg once daily), placebo, and fluticasone propionate (FP; 250, 500, and 1000 µg once daily; 1000 µg twice daily) on 8-hour plasma cortisol levels in healthy volunteers. Reproduced with permission from Grahnen A, Eckernas SA, Brundin RM, Ling-Anderson A. An assessment of the systemic activity of single doses of inhaled fluticasone propionate in healthy volunteers. *Br J Clin Pharmacol* 1994;38:521-5, by Blackwell Science Ltd.).

TABLE I. Factors influencing the occurrence of systemic adverse events with inhaled corticosteroids

- Dose and frequency of administration
- Pharmacokinetics
 - Absorption from lung and gut
 - Clearance rate: first-pass hepatic metabolism and metabolism in lung
- Inhalation techniques
 - Spacer
 - Mouth rinsing
- Host-related factors, e.g., age, inherited factors

8-hour] exogenous adrenocorticotrophic hormone, or metyrapone- or insulin-induced hypoglycemia). Although basal adrenal function can easily be acutely perturbed (over hours to days), clinically relevant suppression of the HPA axis with subsequent adrenocortical atrophy usually requires weeks or months of exogenous glucocorticoid exposure.

One study in which normal volunteers were given multiple doses of beclomethasone dipropionate for 10 days illustrates the variable sensitivities of different tests of HPA axis function.² Changes in single measurements of morning plasma cortisol were least sensitive and only showed significant suppression compared with placebo at the highest inhaled dose (2000 µg/day) of BDP. In contrast, HPA axis function, assessed by either 24-hour urinary free cortisol or the response to metyrapone, showed significant suppression at doses of BDP as low as 800 µg/day.

CLINICAL RELEVANCE OF HPA AXIS SUPPRESSION

When analyzing the results of HPA axis suppression with inhaled corticosteroids, it is important to define the

TABLE II. Factors influencing the incidence of adrenal suppression with inhaled corticosteroids

- Dose and frequency of administration
- Timing of dose(s)
- Duration of treatment
- Prior long-term systemic steroid use
- Population studies:
 - Healthy vs asthmatics
 - Pediatric vs adults
- Significant interindividual variability
- Adrenal function tests used

study end points as well as the clinical implications of the findings (Table III). For example, the low-dose (1 µg) ACTH test is more sensitive than the standard (250 µg) short ACTH test to detect mild adrenocortical atrophy because physiologic rather than pharmacologic doses of ACTH are administered.³ While this test may be clinically relevant in the evaluation of patients with pituitary tumors, it is more likely to be a research tool to define threshold and dose-related subtle adrenocortical suppression in patients taking inhaled corticosteroid compounds.

One study in healthy volunteers demonstrates this key issue of clinical relevance of HPA axis suppression after single-dose inhalation of three doses (250, 500, or 1000 µg) of FP and one dose (800 µg) of BUD at 11 PM.⁴ Plasma cortisol profiling was performed every 2 hours, morning cortisol levels were measured, and areas under the curve were calculated. Although the study design exaggerated HPA suppression with FP, because high doses were used and the inhalation was administered late in the day, the results nevertheless illustrate a number of important points. First, there was an expected dose-related reduction in mean morning cortisol levels and AUC after evening administration of FP; the wide interindividual variation in responses is also shown in Fig. 1. Second, the differing potency of these two compounds was apparent, with FP being about twice as potent as BUD on a microgram-per-microgram basis. Finally, and of great clinical relevance, cortisol suppression was partial at the low and medium doses of FP.

From a physiologic point of view, the inhaled compound supplies a fraction of the daily glucocorticoid requirement, whereas endogenous cortisol production is largely preserved. For example, if the starting dose of an inhaled corticosteroid results in a documented 10% to 20% reduction in cortisol, this means that 10% to 20% of the daily glucocorticoid requirement is supplied by the inhaled compound; that is, 80% of endogenous cortisol production is preserved. In these individuals, in whom the total glucocorticoid equivalent supplied and produced is normal, there should be no risk of adrenal crisis or systemic toxicity to other tissues such as bone. Thus by simple arithmetic (inhaled steroid contribution + endogenous cortisol production = normal), the total physiologic glucocorticoid requirement is not ex-

TABLE III. Clinical assessment of HPA axis suppression

End-point assessment of HPA axis suppression	Functional status of HPA axis
Statistical significance	Normal
Physiological perturbation	Partial suppression
Clinical relevance	Complete suppression (adrenocortical atrophy)

ceeded at lower or middle dosage levels of inhaled corticosteroids. Consequently, at low/medium dosage levels of inhaled corticosteroids, the HPA axis is minimally and partially suppressed, and it is only at high dosage levels of any inhaled corticosteroid that the daily glucocorticoid requirement is provided solely or exceeded by the inhaled corticosteroid. In such circumstances, the HPA axis will be significantly suppressed and the adrenal cortex will become atrophic after long-term high-dose administration of inhaled corticosteroid. If the inhaled corticosteroid was abruptly withdrawn, such patients might theoretically also be at risk of acute adrenal insufficiency, particularly in the presence of concomitant stress, such as sepsis.

In contrast to the effects of acute administration of FP over several hours, the cortisol response was assessed with a 6-hour exogenous ACTH infusion in patients with asthma after treatment with either prednisone 10 mg/day or two doses (300 or 500 μ g twice daily) of triamcinolone acetone (TAA) or two doses (100 or 500 μ g twice daily) of FP for 1 month (data on file, Glaxo Wellcome). No suppression occurred in any of the inhaled corticosteroids treatment groups, but prednisone caused significant suppression compared with the inhaled corticosteroids groups ($p < 0.05$) (Fig. 2). This type of study demonstrates that compared with inhaled corticosteroids, systemic steroids have greater toxicities and side effects as the result of their poor topical/systemic therapeutic ratios. In this context of treatment duration, the long-term study of Volovitz and coworkers was particularly reassuring; in this study, inhaled BUD 200 μ g/day for 5 years was not associated with HPA axis suppression (assessed by morning cortisol and short ACTH stimulation tests) in any of the 15 pediatric patients.⁵ This type of study is necessary to document that long-term use of an inhaled corticosteroid at a particular dose range is associated with minimal or no HPA axis suppression.

HIGH-DOSE INHALED CORTICOSTEROID AND HPA AXIS SUPPRESSION

Few published studies have addressed the issue of HPA axis suppression in patients with asthma during long-term, high-dose treatment with inhaled corticosteroids. The cross-sectional report of Brown et al. evaluated morning cortisol, urinary free cortisol, and short ACTH stimulation testing in 74 patients with asthma who had been treated with a median dose of 1600 μ g of either BDP or BUD for a median duration of 13

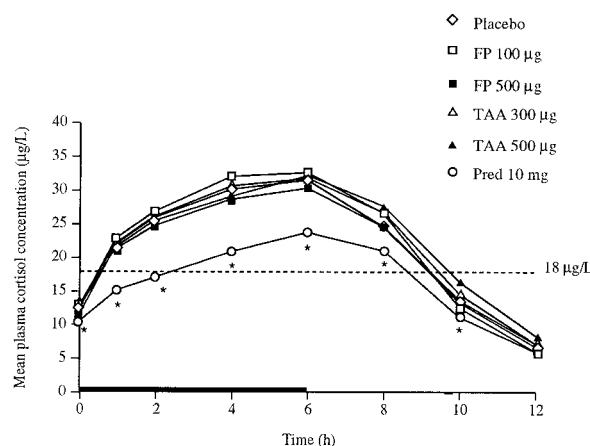


FIG. 2. Effect of placebo, fluticasone propionate (FP; 100 and 500 μ g twice daily), triamcinolone acetone (TAA; 300 and 500 μ g twice daily), and prednisone (Pred; 10 mg daily) on plasma cortisol levels in asthma patients (data on file, Glaxo Wellcome).

TABLE IV. Conclusions and recommendations for treatment with inhaled corticosteroids

- Low/medium doses of inhaled corticosteroids:
 - Iatrogenic Cushing's syndrome absent
 - Partial inhibition of HPA axis (no risk of adrenal crisis)
- High doses of inhaled corticosteroids:
 - Iatrogenic Cushing's syndrome reported
 - Variable HPA axis suppression (significant interpatient variability)
- Because of the risk of impaired pituitary-adrenal response during significant concurrent illness (e.g., sepsis) in some patients taking high-dose inhaled corticosteroids, the following groups should be considered for treatment with additional systemic glucocorticoids:
 - Adults receiving >1500 μ g/day of BDP, BUD, FLU, TAA, or FP
 - Children receiving >400 μ g/day of BDP, BUD, FLU, TAA, or FP
 - All patients with Cushingoid stigmata
 - All patients previously treated with long-term oral steroids

FLU, Flunisolide; TAA, triamcinolone acetone.

months.⁶ Approximately 30% of these patients had received prior courses of steroids, but such treatment was prohibited within 6 months of HPA axis evaluation. The results of this high-dose inhaled corticosteroid study showed that 80% of patients did not exhibit HPA axis suppression; in the remaining 20% of patients, HPA axis suppression was correlated with the duration of inhaled corticosteroid use as well as prior systemic steroid exposure. One implication of this study is that patients with prior long-term systemic steroid exposure could also have HPA axis suppression sustained by high-dose inhaled corticosteroid treatment.

Another high-dose inhaled corticosteroid study investigated the cortisol response to the stress of an asthma exacerbation by evaluating whether 13 patients with

asthma, who had been treated with either BUD or BDP 1500 to 2400 $\mu\text{g}/\text{day}$ for 2 to 16 years, could mount a cortisol response similar to that achieved during insulin tolerance testing (i.e., a cortisol level $>18 \mu\text{g}/\text{dl}$).⁷ The comparator group comprised 7 patients who had never received inhaled corticosteroids; severity of asthma exacerbation was estimated by the forced expiratory volume in the first second ($\text{FEV}_{1\text{f}}$) and measurement of arterial blood oxygen pressure (PaO_2) in the emergency room. Nine of 20 patients failed to achieve a cortisol level $>18 \mu\text{g}/\text{dl}$, including 3 patients who had never been exposed to inhaled corticosteroids. There was no dose-response relationship in the 6 inhaled corticosteroid-treated patients who failed to achieve a cortisol level $>18 \mu\text{g}/\text{dl}$; these patients also appeared less stressed (i.e., had higher PaO_2 levels). Such studies emphasize that the risk of acute adrenocortical insufficiency is probably low, even in patients receiving high-dose inhaled corticosteroid treatment.

RISK OF ADRENAL CRISIS

Finally, the risk of acute adrenal insufficiency culminating in adrenal crisis in patients taking steroids (systemic and/or inhaled corticosteroids) is probably exaggerated. There are several studies of patients taking long-term systemic steroids in which treatment was withheld for 36 hours (before and during major surgeries); cortisol levels and blood pressure were recorded during and after surgery. Despite subnormal cortisol responses in a large number of patients, hypotension was extremely uncommon and did not correlate with measured cortisol levels.^{8,9} The implication of these studies is that at low/medium doses of inhaled corticosteroids, in which there is minimal/modest HPA axis suppression, there should be no risk of adrenal crisis even under stressful situations.

CONCLUSIONS

HPA axis suppression should be viewed as a marker of the systemic bioavailability of inhaled corticosteroids, and the focus should be on the clinical relevance of these

alterations (Table IV). The clinical relevance of inhaled corticosteroid treatment at a defined dose should also be viewed in the context of HPA axis suppression after long-term inhaled corticosteroid use, that is, months rather than days, because adrenocortical atrophy usually requires weeks or months of exogenous glucocorticoid exposure. Although idiosyncratic responses may occur at medium doses of inhaled corticosteroids, more clinically relevant HPA axis suppression (and accompanying adrenocortical atrophy) should only be expected after high-dose, long-term treatment in a subset of patients. Prior use of long-term systemic steroids is also a risk factor for adrenal atrophy. Recommendations for systemic steroid supplementation during stress in such patients, for example, sepsis, are outlined in Table IV.

REFERENCES

1. Barnes PJ. Inhaled glucocorticoids for asthma. *N Engl J Med* 1995;332:868-75.
2. Padfield PL, Teelucksingh S. Inhaled corticosteroids: the endocrinologist's view. *Eur Respir Rev* 1993;3:494-500.
3. Tordjman K, Jaffe A, Grazas N, Apter C, Stern N. The role of low dose (1 microgram) adrenocorticotrophin test in the evaluation of patients with pituitary diseases. *J Clin Endocrinol Metab* 1995;80:1301-5.
4. Grahnen A, Eckernas SA, Brundin RM, Ling-Andersson A. An assessment of the systemic activity of single doses of inhaled fluticasone propionate in healthy volunteers. *Br J Clin Pharmacol* 1994;38:521-5.
5. Volovitz B, Amir J, Malik H, Kauschansky A, Varsano I. Growth and pituitary-adrenal function in children with severe asthma treated with inhaled budesonide. *N Engl J Med* 1993;329:1731-3.
6. Brown PH, Blundell G, Greening AP, Crompton GK. Hypothalamo-pituitary-adrenal axis suppression in asthmatics inhaling high dose corticosteroids. *Respir Med* 1991;85:501-10.
7. Brown PH, Blundell G, Greening AP, Crompton GK. High dose inhaled steroid therapy and the cortisol stress response to acute severe asthma. *Respir Med* 1992;86:495-7.
8. Toogood JH, Jennings B, Baskerville J, Lefcoe NM. Personal observations on the use of inhaled corticosteroid drugs for chronic asthma. *Eur J Respir Dis* 1984;65:321-38.
9. Kehlet H, Binder C. Adrenocortical function and clinical course during and after surgery in unsupplemented glucocorticoid-treated patients. *Br J Anesth* 1973;45:1043-8.