

Effects of intranasal corticosteroids on the hypothalamic-pituitary-adrenal axis in children

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In adults, morning plasma cortisol levels are twice that of late afternoon and evening values. In children, a delay in the time of onset in peak cortisol levels has been observed in those treated with inhaled corticosteroids. Consequently, the single morning cortisol level has a low sensitivity for detecting adrenal insufficiency in children. It is not clear which test is best for detection of clinically relevant hypothalamic-pituitary-adrenal (HPA) axis suppression in children; 24-hour plasma cortisol is a good test because it measures biologically active, free cortisol levels for the entire day and is noninvasive. For research purposes, the 24-hour integrated concentration plasma cortisol test is preferred. Studies that have looked at HPA axis suppression with intranasal corticosteroids indicate that overall, intranasal corticosteroids have minimal effect on the HPA axis. A review of the literature reveals one study in which there was a decreased output of urinary cortisol during treatment with either budesonide or fluticasone propionate in adults. Other studies of fluticasone propionate or budesonide have shown no effect on the HPA axis in children. Beclomethasone dipropionate was shown to affect urinary cortisol output in one study of healthy volunteers. However, in a long-term study in children, no effect on the HPA axis was found. Mometasone furoate has been extensively studied in more than 20 trials of adults and children. No effects on the HPA axis were detected in either children or adults. It is unlikely that children are more sensitive to corticosteroids than are adults. There seems to be little point in performing routine monitoring of adrenal function in children who are treated with intranasal corticosteroid treatment. (*J Allergy Clin Immunol* 2001;108:S32-9.)

Key words: Adrenal corticotrophic hormone, beclomethasone dipropionate, cortisol, flunisolide, fluticasone propionate, corticosteroid, intranasal corticosteroid, hypothalamus, mometasone furoate, triamcinolone acetonide

The effectiveness of intranasal corticosteroids (INCS) in the treatment of allergic rhinitis (AR) is well established. When administered systemically, corticosteroids are associated with a number of adverse effects. However, INCS have been designed to both optimize topical

Abbreviations used

ACTH:	Adrenocorticotrophic hormone
AR:	Allergic rhinitis
AUC:	Area under the curve
BDP:	Beclomethasone dipropionate
BMP:	Beclomethasone monopropionate
BUD:	Budesonide
CRF:	Corticotropin releasing factor
FLU:	Flunisolide
FP:	Fluticasone propionate
HPA:	Hypothalamic pituitary adrenal
MF:	Mometasone furoate
IC:	Integrated concentration
INCS:	Intranasal corticosteroids
ITT:	Insulin tolerance test
TAA:	Triamcinolone acetonide

effects and minimize systemic effects, although there are differences among the INCS in these properties. Because INCS are widely used in adults and children, the issues of safety and the ratio of risk to benefit assume primary importance.

The occurrence and severity of side effects with INCS depend on a large number of variables, including the characteristics of the drug (lipophilicity, pharmacokinetics, pharmacodynamics) as well as dosage and susceptibility of the patient. In general, systemic side effects from INCS do not represent a problem in adult subjects.¹ The dosage used intranasally is less than that usually prescribed for asthma therapy; therefore, the risk of systemic adverse effects is lower with INCS than inhaled corticosteroids. However, the risk may be greater in patients receiving intranasal and inhaled corticosteroids concomitantly for the treatment of rhinitis and asthma.² Because the percentage of corticosteroid subjected to first-pass metabolism after intranasal administration is less than that after inhalation, the contribution of the intranasal dose to the total systemic concentration becomes of greater significance. In addition, children may receive higher dosages of corticosteroid, on a $\mu\text{g}/\text{kg}$ basis, than adults.³

Long-term treatment with corticosteroids may result in a significant suppression of the hypothalamic-pituitary-adrenal (HPA) axis, which is a systemic effect that can be monitored. Corticosteroid derivatives mimic the natural corticosteroid hormone, cortisol, mainly through interactions with the glucocorticoid receptor, and as such may interfere with the activity of the HPA axis,

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which largely determines the rate of cortisol production.⁴ Treatment with corticosteroids can reduce adrenal corticotrophic hormone (ACTH) production. This in turn leads to reduced cortisol secretion by the adrenal glands. If this sequence of events continues, atrophy of the adrenal gland, sometimes associated with adrenal insufficiency (eg, in response to stress), can result (Fig 1). This article will focus on the evaluation of HPA axis function and the effect of INCS on the HPA axis in children.

ASSESSING THE INTEGRITY OF THE HPA AXIS

Measurements of HPA axis activity are more sensitive than biochemical indexes of bone metabolism for detecting systemic bioactivity of inhaled corticosteroids. A measurable systemic effect may be associated with a clinically relevant systemic side effect, but this is not always the case. In general, there are two broad categories of tests that measure HPA axis activity: those that monitor basal adrenal function and those that monitor reserve function. Tests to evaluate basal function of the adrenal glands include morning plasma cortisol levels, urinary-free cortisol levels over 24 hours, overnight urinary cortisol excretion, 24-hour integrated area under the curve (AUC) plasma cortisol levels, and nocturnal integrated plasma cortisol. Tests providing some indication of reserve function of HPA axis include ACTH cosyntropin stimulation, the corticotropin releasing factor (CRF) test, the metyrapone test, and insulin-induced hypoglycemia (Table I).⁴

Basal adrenal function tests

Morning plasma cortisol. The concentration of plasma cortisol is normally regulated by the concentration of plasma ACTH, which follows a circadian rhythm originating in the central nervous system (Fig 1). The highest concentrations of plasma cortisol range from 275 to 555 nmol/L (10 to 20 µg/dL) and are seen in the early morning, within 1 hour of the usual time of awakening. At 4 PM, plasma cortisol concentrations range from 85 to 275 nmol/L (3 to 10 µg/dL). The lowest levels, less than 140 nmol/L (5 µg/dL), are observed 1 hour after the usual time for going to sleep. The morning plasma cortisol peak may vary from 5 to 9 AM, and this helps to account for the variation in 8 AM plasma cortisol concentration between 150 nmol/L and 700 nmol/L. An additional factor that influences cortisol levels is the delay in the time of onset in cortisol peak observed in children treated with inhaled corticosteroids.⁵

Because of these wide intersubject and intrasubject variations, the single morning cortisol level has a low sensitivity for detecting adrenal insufficiency. The basal cortisol level does not adequately predict the response to ACTH or the insulin-induced hypoglycemia test.⁶ Additionally, the 24-hour urinary-free cortisol may decrease without any change in morning plasma cortisol level.⁷

The measurement of a single plasma level of ACTH at 8 AM is more variable and of even less value than a sin-

gle measurement of plasma cortisol at the same time, because ACTH release is pulsatile throughout the night.⁸

Urinary-free cortisol excretion The urinary-free cortisol test is more widely used by endocrinologists to investigate suspected adrenal hyperfunction; it is less widely used to measure potential hypofunction. Most cortisol is excreted in the urine as metabolites, with only a small fraction excreted as free cortisol. Cortisol metabolites can be quantified colorimetrically as 17-hydroxycorticosteroids, as 17-oxogenic corticoids, or measured individually after separation by capillary column gas chromatography. The excretion rates of these metabolites are influenced by changes of hepatic function and renal clearance. Cortisol circulates in the blood primarily bound to proteins (cortisol-binding globulin and albumin), so that only 5% of the total cortisol in the blood circulates as free hormone. In the renal glomeruli, free cortisol is filtered from the bloodstream and not reabsorbed by the renal tubules. A proportion of cortisol is thus excreted in the urine (50 to 300 nmol/24 h). Ideally, free corticosteroids should be extracted from the urine before quantitative analysis, so that only nonconjugated corticosteroids are recovered and the quantitatively dominant corticosteroid conjugates are eliminated.⁹

The measurements of urinary-free cortisol excretion rates are often used as an index of adrenal suppression because the activity of the adrenal gland can be integrated over 24 hours. It has been suggested that an inhaled corticosteroid has influenced the HPA axis if urinary cortisol excretion is less than 30 to 40 nmol/L/m per 24 hours.¹⁰ A value greater than 100 nmol should exclude clinically important HPA axis suppression.¹¹ If a lower result is obtained, the adequacy of collection needs to be ascertained, renal function should be assessed, and a cosyntropin stimulation test may be performed.

However, the variability of urinary cortisol assays can be high, and there may be problems in relying on the accuracy of the urine collections, particularly in children. If urine collection is done properly, a close correlation is observed between 24-hour urinary-free cortisol secretion and the maximum serum cortisol level achieved during insulin stress,¹¹ the test that is preferred by endocrinologists to evaluate the function of the HPA axis.⁶

Properly performed, the 24-hour urinary-free cortisol test is particularly relevant to the assessment of adrenal activity because it effectively measures the biologically active plasma-free cortisol level for the entire day.⁷ It also has the advantage of being a noninvasive technique. The use of timed fractionated collections to measure urinary-free cortisol excretion has been investigated to obviate compliance and variability problems associated with a 24-hour collection. An overnight and first waking collection of urinary-free cortisol is simple for the patient to collect and is as sensitive as a 24-hour collection when corrected for creatinine excretion.¹²

24-hour or overnight integrated concentration of plasma cortisol. The 24-hour integrated concentration (IC) or overnight IC of plasma cortisol has been suggested to be a sensitive test of HPA axis function.¹³ With this test, blood is collected every 30 minutes during a 24-hour

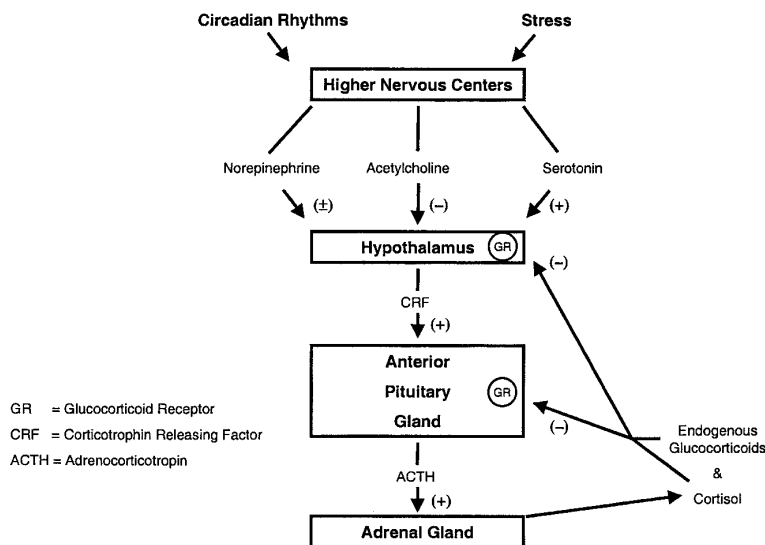


FIG 1. Neuroendocrine pathways involved in HPA axis.

TABLE I. Tests for evaluating HPA axis function

Test	Comments	Sensitivity
Basal adrenal function		
Morning plasma cortisol	Wide intersubject and intrasubject variation in time of onset and level of cortisol peak	Low
24-h Urinary-free cortisol	Problems with accuracy of urine collection	Medium to high
Overnight urinary-free cortisol	Simple in cooperative patients	Medium to high
24-h/overnight IC plasma cortisol	Invasive, may detect changes or delay in the circadian rhythm	High
Reserve adrenal function		
Cosyntropin test	Pharmacologic (high-dose) stimulation, physiologic (low-dose) stimulation, allergic reaction possible	Medium
CRF test	Results not always interpretable	Medium
Metirapone test	Unpleasant side effects	High
Insulin tolerance test	Potentially dangerous, unpleasant side effects	High

period by means of a nonthrombogenic constant blood withdrawal system in a hospital setting.

The 24-hour IC of plasma cortisol has been shown to be a more sensitive test of HPA axis function than the 24-hour urinary excretion of 17-hydroxycorticosteroids or free cortisol for differentiating patients with Cushing syndrome or hypertension from normal individuals,¹⁴ and for the evaluation of HPA axis activity in asthmatic patients receiving inhaled corticosteroids.¹⁵ Multiple sampling at frequent time intervals gives a better picture of HPA axis function and may detect a change or a delay in the circadian rhythm. This method detects small reductions in the frequent peaks of plasma cortisol concentration that normally occur in patients at rest. The small plasma cortisol peaks are the first to disappear in the sensitive feedback system of the HPA axis.⁵ However, the clinical relevance of these findings is not known because the test may detect changes resulting from corticosteroid doses that have been used for years

without any clinical side effects. Moreover, it is an alternative test for selected patients only and cannot be used for routine monitoring of children treated with inhaled corticosteroids.

Reserve adrenal function tests

Cosyntropin stimulation test. In the standard cosyntropin stimulation test, plasma cortisol measurements are made immediately before and 30 minutes after injection of 250 µg of a synthetic peptide with the same potency in stimulating the adrenal gland as ACTH. Cosyntropin consists of amino acids 1 through 24 of the ACTH molecule, a 39-amino-acid peptide. Plasma cortisol concentration will increase in much the same way as in the insulin test.⁶ An increase in cortisol concentration of 200 nmol/L over baseline for a sample taken 30 minutes after injection of cosyntropin is considered normal if the actual concentration rises to 550 to 1100 nmol/L.^{4,6} The cosyntropin stimulation test should be

performed at approximately 9 AM, after the usual morning dose of corticosteroid.

If the adrenal gland is suppressed over a long period of time, there may be a reduced adrenal response to ACTH. The effect of corticosteroids is mediated by the hypothalamus and pituitary gland to produce secondary hypoadrenalism (Fig 1). Reduced adrenal activity results from corticosteroid-induced hyposecretion of endogenous ACTH, and it is inappropriate to assess the systemic effect of an inhaled corticosteroid by measuring the direct response of the adrenals to exogenous synthetic trophic hormone. It is likely that effects on the cosyntropin stimulation test during inhaled corticosteroid treatment are confined to individuals who have secondary adrenal changes. This would account for the discrepancy seen between the cosyntropin stimulation test and other methods of assessing HPA axis function in some studies.^{7,16} The cosyntropin stimulation test is contraindicated in patients who are allergic to the peptide, and resuscitation equipment should be available in the event of anaphylactic reaction.

A second cosyntropin stimulation test has been suggested, and it uses a relatively low physiologic dose (0.5 µg) of the synthetic ACTH peptide.¹⁷ Although this experimental test appears to be somewhat more sensitive than the standard cosyntropin test, it has the same basic problems as basic standard cosyntropin testing and is not as accurate as overnight urinary cortisol determinations.^{18,19}

Corticotropin releasing factor tests. During stress, the hypothalamus secretes CRF, which subsequently stimulates the release of ACTH from the pituitary (Fig 1). Therefore, CRF tests (injection of 100 µg CRF) have the advantage of evaluating the status of the anterior pituitary gland as well as the adrenal cortex. A normal increase in ACTH (7 pmol/L) occurs 15 to 30 minutes after injection of CRF. The corresponding normal increase in cortisol is observed at 30 to 60 minutes. In this case, the peak cortisol value should be 550 nmol/L, or a 1.5-fold rise in the basal level to a value of at least 276 nmol/L.²⁰ The response to CRF is not always interpretable, most likely because of the erratic delivery of the exogenous hypothalamic factor from the peripheral circulation to the pituitary.

Insulin tolerance test. The ability of the HPA axis to respond to stress can be mimicked by inducing hypoglycemia with the injection of insulin. Hypoglycemia induces a strong stress response, resulting in an increase in ACTH. Thirty minutes after the injection, there will be a rise in the plasma cortisol concentration if adrenal function is normal.⁶

Even though the insulin tolerance test (ITT) represents a sensitive method of assessing the integrity of the HPA axis, it is expensive and contraindicated in children younger than 5 years of age, in individuals with cerebrovascular or cardiovascular diseases, or individuals with a history of seizures. The time-consuming, potentially dangerous nature of this test as well as the unpleasant side effects render the insulin tolerance test impractical as a screening test for assessment of safety of corticosteroids.

The metyrapone test. The pituitary-adrenal response to a single dose of metyrapone is a sensitive estimation of the HPA axis function.²¹ Metyrapone inhibits 11β-hydroxylase, an enzyme essential for cortisol synthesis, thereby reducing plasma cortisol and subsequently increasing ACTH secretion from the pituitary gland. The response is evaluated by measuring plasma 11-deoxycortisol (the substrate for 11β-hydroxylase) or its metabolites in the urine. The single-dose metyrapone test and the insulin-induced hypoglycemia test have been shown to provoke a similar degree of ACTH release.²² The test is seldom used, however, because of the unpleasant side effects induced by the drug such as nausea, dizziness, and vomiting.

Effect of nasal corticosteroids on the HPA axis

Fluticasone propionate. In adult patients with perennial rhinitis, the administration of 200 µg fluticasone propionate (FP) once daily for 1 year did not significantly affect the HPA axis, as assessed by plasma cortisol and 24-hour urinary-free cortisol collected during and after a 6-hour cosyntropin challenge.²³ In 249 children with seasonal AR, 100 µg FP (half the adult dose) or 200 µg administered once a day for 4 weeks did not affect the 24-hour urinary excretion of free cortisol.²⁴ No effect on urinary-free cortisol was demonstrated with nasal 200 µg FP once daily for 6 weeks in adult patients.²⁵ Mean morning plasma cortisol concentrations were within the normal range and were similar before and after treatment with 200 µg FP once a day or 168 µg beclomethasone dipropionate (BDP) twice a day, or placebo for 2 weeks in adult patients with seasonal AR.²⁶ Similar results have been observed in 250 children treated with 100 µg or 200 µg FP once a day for 14 days (Table I).²⁷

In 14 normal subjects, 2 weeks of treatment with FP (200 µg once daily the first week then twice daily the second week) or budesonide (BUD) (400 µg once daily the first week, then twice daily the second week) was associated with a decreased output of urinary cortisol during the course of treatment with FP and BUD, with no statistical difference between the two drugs (Table II).²⁸ The ITT, however, showed a normal response, indicating that the HPA axis was not totally suppressed and that the observed systemic effects were within a biological and physiologic range.²⁸ In 16 healthy volunteers, 200 µg FP once a day for 4 days induced a significant suppression of urinary cortisol excretion. There was, however, no blunting of the response to ACTH (0.5 µg) stimulation.¹⁸

Budesonide. A 12-month treatment period with BUD or BDP (400 µg/d) was not associated with significant changes in plasma cortisol levels.²⁹ Overnight urinary cortisol was not affected by BUD treatment with 100 µg or 200 µg once daily in each nostril for 4 weeks in 83 children with seasonal AR.³⁰ Plasma cortisol analysis before and after challenge with ACTH (250 µg) revealed no influence on HPA axis function in 104 adult patients with perennial rhinitis treated for 12 months with 200 µg/d or 400 µg/d.³¹ Urinary cortisol

TABLE II. Effect of intranasal corticosteroids in healthy volunteers

Type of steroid (dose)	Effect on HPA axis	References
BDP (400 µg twice daily for 4 d)	Decreased urinary cortisol	32
BUD (200 and 400 µg twice daily for 4 d)	Decreased urinary cortisol	32
BUD (400 µg daily the first week, then twice daily the second week)	Decreased urinary cortisol; normal response to insulin test	27
FP (200 µg daily the first week, then twice daily the second week)	Decreased urinary cortisol; normal response to insulin test	27
FP (200 µg daily for 4 d)	Decreased urinary cortisol; normal response to cosyntropin (0.5 µg) stimulation test	28
MF (single dose of 4000 µg or 200-400 µg daily for 36 d)	No effect on cosyntropin (250 µg) stimulation test	46, 47

was significantly decreased in healthy volunteers by 200 µg and 400 µg BUD administered twice a day for 4 days (Table II).³²

Beclomethasone dipropionate. BDP was introduced first as a nasal spray then as an aqueous suspension and most recently as an inhalational dry powder. Although most corticosteroids achieve their effects through the actions of the parent compound, there is evidence that BDP is metabolized to form the active metabolites beclomethasone 17-monopropionate (17-BMP) and beclomethasone 21-monopropionate (21-BMP). This is an activation step for BDP, with the majority of its activity thought to be the result of the more potent metabolite, 17-BMP.³³ A recent review encompassing the past 30 years of literature uncovered only one documented case of adrenal suppression with intranasal BDP.³⁴ This suggests that intranasal doses of BDP of up to 400 µg per day are not associated with any suppressive effect on the HPA axis.³⁴ In a review of more than 200 studies, BDP did not produce systemic side effects, even with prolonged use of up to 6 years.³⁵

In a study involving 100 children, 168 µg BDP nasal spray twice daily or placebo for up to 12 months did not show any effect on HPA axis evaluated by a 60-minute cosyntropin stimulation test done at baseline and at the 6- and 12-month visits.³⁶ BDP treatment, either 400 µg/d or 800 µg/d for 4 weeks in children with AR, was not associated with suppression of the HPA-axis response to lysine-vasopressin stimulation.³⁷ In healthy volunteers, 400 µg BDP twice daily for 4 days decreased urinary cortisol output.³² However, the study was performed in selected subjects with a proven ability to show cortisol suppression after treatment with a single evening dose of oral prednisone. Notably, in a study lasting 1 year, children with perennial rhinitis treated with 168 µg BDP twice daily were found to have slowed growth compared with a similar group treated with placebo.³⁸

Flunisolide. Flunisolide (FLU) has a high bioavailability when administered to normal subjects (50% of an inhaled dose reaches the systemic circulation).³⁹ To the best of our knowledge, no study is available on the effect of nasal FLU on HPA axis function.

Triamcinolone acetonide. No significant effect of 220 to 440 µg/d triamcinolone acetonide (TAA) aqueous

nasal spray for 6 weeks was observed on urinary-free cortisol and in the response to cosyntropin (250 µg) stimulation test in adult male subjects.⁴⁰ Furthermore, no major changes in morning cortisol levels have been reported in 93 patients with AR, treated with different dosages (110, 220, 440 µg/d) for more than 1 year.⁴¹ The safety of this drug in patients with AR was further confirmed in two medium-term studies in adult patients.^{42,43} In adults, there is no significant additive adrenal suppression with 220 µg inhaled TAA once daily in patients with asthma already receiving inhaled TAA therapy (800 µg twice daily), but the adrenal suppression was already induced by the asthma treatment.⁴⁴ In pediatric patients with AR, 220 or 440 µg TAA aqueous nasal spray, once daily for 6 weeks, has no measurable effect on adrenocortical function evaluated by plasma cortisol levels after a 1-hour intravenous cosyntropin stimulation.⁴⁵ Furthermore, measurement of TAA concentration in plasma over a 6-hour period demonstrated a rapid decline of the drug and no accumulation of TAA during 6 weeks of treatment.⁴⁵ No studies have been conducted to date in children given TAA.

Mometasone furoate. No detectable effect of mometasone furoate (MF) on the HPA axis was reported in a review of more than 20 clinical trials involving more than 6000 patients treated with MF even at up to 20 times the recommended daily dose (Table II).⁴⁶ In adult volunteers, a single dose of 4000 µg,⁴⁷ or a 36-day treatment with 200 µg to 400 µg once daily in adults⁴⁴ did not show any effect on adrenal function as evaluated with cosyntropin stimulation. In 96 children 3 to 12 years of age, AR treatment with MF at 50 µg, 100 µg, or 200 µg or placebo once daily for 7 to 14 days did not alter HPA axis function evaluated by 24-hour urinary-free cortisol and response to cosyntropin (250 µg) stimulation.⁴⁸ There was no difference between doses nor between active treatments and placebo. In this study, plasma MF concentrations were undetectable in 98% of samples, as assessed by an assay with a lower limit of quantification of 50 pg/mL.⁴⁸ No differences in mean plasma cortisol responses to cosyntropin stimulation were observed in 679 children randomly assigned to receive one of the following for 4 weeks: 25 µg MF, 100 µg MF, 200 µg MF once daily, BDP twice daily, or placebo.⁴⁹

Recently, a 4-way, cross-over, placebo-controlled trial of 20 adult patients with AR was conducted. Patients were randomly assigned and treated once a day for 5 days with placebo or 220 µg TAA, 200 µg MF, or 200 µg BUD. There was no significant difference between placebo and the active treatments in the 24-hour AUC plasma cortisol or in 24-hour urinary cortisol:creatinine ratio, and the diurnal circadian rhythm was unaffected.⁵⁰ In a 1-year study comparing 100 µg MF nasal spray once daily with placebo nasal spray, there was no evidence of growth retardation in the MF-treated group.⁵¹

DISCUSSION

Despite numerous studies of HPA axis function in children treated with INCS, it is unclear which test best detects clinically relevant HPA axis suppression.¹¹ Furthermore, the component of the HPA axis most vulnerable to suppression by exogenous corticosteroid administration is not known. However, it appears that suppression may occur at the level of the hypothalamus or the pituitary or adrenal glands.⁵² Prospective studies comparing basal levels of cortisol (24-hour urinary or plasma cortisol), the cosyntropin stimulation test, ACTH responses to CRF, and stimulation of the hypothalamus (insulin tolerance or metyrapone tests) might better clarify the mechanisms by which inhaled corticosteroids produce HPA axis suppression.¹¹ In assessing which test to use, consideration should be given to costs and possible side effects. One of the more reproducible and practical screening measurements in clinical practice is the overnight urinary-free cortisol collection. This may be further refined by correcting for creatinine and can be used in both adults and children.⁸ A dynamic stimulation test can be used to evaluate adrenal reserve. For research purposes, it would be useful to use the 24-hour integrated concentration of the plasma cortisol test.⁵³

Although there is considerable interindividual variability in adrenal suppression at a given dose of inhaled corticosteroids, in general, the effects on HPA axis suppression are minimal below 800 µg/d in adults and below 400 µg/d in children. For this reason, INCS, given in recommended dosages, are not expected to cause major suppression of HPA axis. However, individuals may differ in their susceptibility to the systemic adverse effects of intranasal corticosteroids, and different corticosteroids formulations and delivery systems may have different effects, particularly in patients receiving concomitant treatment with intranasal and inhaled corticosteroids for AR and asthma, respectively.

Differences in the systemic activity of INCS are likely to be related to the pharmacokinetics of the drug; the dose administered per kilogram of body weight; the duration, frequency, and time of day of the treatment; the site of deposition (gastrointestinal tract as opposed to the nose or the lung); and individual differences in corticosteroid response between different patients. It is unlikely that children are more sensitive than adults to the inhibitory effect of corticosteroids on the HPA axis. It has been

demonstrated that children metabolize BUD (the only corticosteroid for which pharmacokinetic data are available in children) approximately 40% faster than adults do.^{54,55} When comparing systemic effects of intranasal corticosteroids in adults and children, it is important to relate results to the dosage per kilogram of body weight. On a µg/kg basis, children may receive higher dosages than adults. Furthermore, because of differences in affinity for the corticosteroid receptor of different inhaled corticosteroids, different drugs should never be compared on the basis of microgram dosage, but only in terms of equipotent dosages.

Thus, apart from rare reports, INCS administered at the recommended dosages do not cause clinically significant suppression of the HPA axis.⁵⁶ As for adults, no cases of clinical adrenal insufficiency have been reported in patients treated only with inhaled corticosteroids,⁵³ and the same is true for INCS treatment.⁵⁶ Six cases of Cushing syndrome have been reported in patients treated with dexamethasone nasal drops.⁵⁷ Therefore, there is little point in performing routine monitoring of adrenal function in children who are treated with nasal corticosteroids in standard pediatric doses. However, it may be appropriate to monitor growth because it was shown that even in the absence of any effect on HPA axis, nasal corticosteroid treatment might result in a small but significant effect on growth in children.³⁶ In children with asthma and AR, treatment with nasal corticosteroids reduces the severity of asthma symptoms and the need for both rescue medication and systemic corticosteroid therapy.⁵⁸ It is possible that nasal corticosteroid treatment reduces the dose of inhaled corticosteroid that is needed for asthma control. To minimize the potential risk for adverse systemic effects, the dosage of corticosteroids should be titrated to the lowest dosage at which effective control of asthma and rhinitis is maintained.⁵⁹

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