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Adrenal Suppression

Krystallenia I Alexandraki, MD, PhD, MSc,MSc, Endocrine Unit, 1st Department of Propaedeutic Medicine, Laiko University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece; alexandrakik@gmail.com
Gregory A Kaltsas, MD FRCP, Endocrine Unit, 1st Department of Propaedeutic Medicine, Laiko University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece, gkaltsas@endo.gr
George P Chrousos, MD, MACP, MACE, FRCP, Unit of Endocrinology, Metabolism and Diabetes, First Department of Paediatrics, National University of Athens Medical School, Athens, Greece, chrousos@gmail.com

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CLINICAL RECOGNITION

Adrenal suppression, a form of secondary adrenal insufficiency (SAI), is a common clinical problem most often due to sudden cessation of chronic exposure to exogenous glucocorticoid administration or, rarely, after correction of endogenous hypercortisolism. It results from the inability of suprahypothalamic and hypothalamic centers of the hypothalamic-pituitary-adrenal (HPA) axis to recover their function and can last from days to months or years, depending on the dose and duration of the exposure to the glucocorticoid and patient's idiosyncrasy. Exogenous glucocorticoids cause decreased secretion of corticotropin-releasing hormone (CRH) and other adrenocorticotropic hormone (ACTH) secretagogues, such as arginine-vasopressin (AVP) and alter the function of higher brain centers that regulate their secretion. Recovery of adrenal function may take as long as 1 to 2 years. In cases of endogenous hypercortisolemia adrenal suppression develops after the removal of a functional adrenal tumor secreting cortisol, or following successful removal of ACTH-secreting pituitary adenoma or other sources of ectopic ACTH secretion. Interestingly, the period to recover from adrenal suppression after the removal of ACTH-secreting pituitary adenoma caused by prolonged suppression of normal corticotrophs may be a predictor of sustained remission.

Regarding the definitions of adrenal insufficiency (AI), it is a disorder characterized by impaired adrenocortical function and decreased production mainly of glucocorticoids. Primary AI (PAI) is characterized, in addition by decreased production of mineralocorticoids (MCs) and/or adrenal androgens that occur in the setting of diseases affecting the adrenal cortex. Secondary AI (SAI) arises in diseases or conditions affecting the pituitary gland and the secretion of ACTH, while the affected hypothalamus resulting in abnormal secretion of corticotropin-releasing hormone (CRH) and other ACTH secretagogues defines the tertiary form of AI (TAI). As adrenal suppression refers to decreases of cortisol secretion from the adrenal *zona fascicularis* the function of *zona glomerulosa* remains normal. Thus,

hyponatremia is the main electrolytic disturbance observed, while circulating plasma potassium, renin, and aldosterone concentrations are within the normal range.

A broad range of severity can be seen as a result of complete or partial HPA axis suppression and concomitant adrenal gland atrophy. The true prevalence of overt adrenal insufficiency (AI) is probably rare as glucocorticoid treatment is gradually tapered before complete discontinuation leaving enough time for HPA axis recovery. However, due to the lack of specific symptoms the exact prevalence of AI following glucocorticoid tapering may be under-reported. Two recent systematic reviews reported that the percentage of patients with AI ranged from 0% to 100%, with a median (IQR) = 37.4% (13–63%), while when the studies were stratified by administration route, the percentages of patients with AI ranged from 4.2% for nasal administration (95% confidence interval [CI], 0.5–28.9) to 52.2% for intra-articular administration (95% CI, 40.5– 63.6); by disease, from 6.8% for asthma with inhalation glucocorticoids only (95% CI, 3.8 –12.0) to 60.0% for hematological malignancies (95% CI, 38.0 –78.6); by the dose from 2.4% (95% CI, 0.6 –9.3) (low dose) to 21.5% (95% CI, 12.0 –35.5) (high dose); by treatment duration from 1.4% (95% CI, 0.3–7.4) (less than 28 days) to 27.4% (95% CI, 17.7–39.8) (more than 1 year) in asthma patients.

The main symptoms of glucocorticoid insufficiency range from anorexia, fatigue, nausea, vomiting, dyspnea, fever, arthralgias, myalgias, and orthostatic hypotension to dizziness, fainting, and circulatory collapse. Hypoglycemia is occasionally observed in children and very thin adult individuals. Since 1-3% of adults worldwide are under long-term glucocorticoid therapy (Table 1), the awareness for adrenal suppression and the associated risk for glucocorticoid deficiency, as well as the appropriate treatment, are important clinical issues.

Table 1: Use of Glucocorticoid Therapy in Clinical Practice	
Long-Standing Treatment	
ENDOCRINE CAUSES	
Replacement therapy	Primary AI Secondary AI
Adrenal suppression Therapy	Congenital adrenal hyperplasia Glucocorticoid resistance
Anti-inflammatory therapy	Grave's opthalmopathy
NON-ENDOCRINE CAUSES	
Immunosuppressive/ anti-inflammatory therapy	Rheumatic diseases- (lupus erythematosus, polyarteritis, rheumatoid arthritis, polymyalgia rheumatica) Skin disorders- (dermatitis, pemphigus) Other autoimmune diseases- (multiple sclerosis, myasthenia Gravis, vasculitis) Hematological disorders- (lymphomas/ leukemias,

	hemolytic anemias, idiopathic thrombocytopenic purpura) Gastrointestinal diseases- (inflammatory bowel disease) Liver diseases- (chronic active hepatitis) Respiratory diseases- (angioedema, anaphylaxis, asthma, sarcoidosis, tuberculosis, obstructive airway disease). Nephrotic syndrome Suppression of host-versus-graft/graft-versus-host reaction- (bone marrow or organ transplantation) Nervous disorders- (cerebral edema, raised intracranial pressure)
Acute Treatment	
ENDOCRINE CAUSES	
Suppression hypothalamic-pituitary-adrenal axis	Cushing syndromediagnostic tests
NON-ENDOCRINE CAUSES	
Several conditions	Acute traumatic spinal cord injury Post-operative additional therapy in severe neurological deficits even after surgery Postoperative pain relief after severe bone operations Fetuses between 24 and 34wk gestation (risk of preterm delivery)
Acute illness or trauma	"Critical illness-related cortisol insufficiency"(CIRCI): vasopressor dependent septic shock and early severe Acute Respiratory Distress Syndrome

AI: adrenal insufficiency

Many synthetic compounds with glucocorticoid activity have been developed in an attempt to maximize the beneficial and minimize the deleterious effects of glucocorticoids. The clinical efficacy of synthetic glucocorticoids depends on their pharmacokinetic, pharmacodynamic and molecular properties, which in turn determine the duration and intensity of glucocorticoid effects. According to their potency synthetic glucocorticoids are subdivided into short-, intermediate-, or long-acting. Treatment modifying factors, such as the age of the patient and the nature and severity of the underlying disease also influence synthetic glucocorticoid effects, duration, and doses administered.

The British National Formulary and the National Institute for Health and Care Excellence Clinical Knowledge Summary, both advise gradual glucocorticoid withdrawal in cases of patients that have received more than 40 mg prednisolone (or equivalent) daily for longer than one week; repeated glucocorticoid doses in the

evening; glucocorticoids for more than three weeks; a short course of glucocorticoids within one year of stopping long-term glucocorticoid therapy; or have other risk factors for adrenal suppression.

PATHOPHYSIOLOGY

Supraphysiologic doses of glucocorticoids given even in small doses and/or for only a few days may result in considerable suppression of the HPA axis by decreasing CRH synthesis and secretion. The trophic and ACTH-releasing effects of CRH on pituitary corticotrophs are attenuated and the synthesis of propiomelanocortin (POMC), ACTH, and other peptides, are substantially decreased. In the absence of ACTH, the adrenal cortex temporarily loses the ability to produce cortisol, and when treatment with glucocorticoids is abruptly stopped transient glucocorticoid insufficiency ensues. It has been reported that the suppression of the HPA axis induced by exogenous glucocorticoids may persist for 6 to 12 months or rarely even longer, after treatment is withdrawn.

DIAGNOSIS and DIFFERENTIAL DIAGNOSIS

To support the diagnosis of adrenal suppression, several predictors of glucocorticoid-induced HPA axis hypofunction have been suggested the best being the duration and dosage of exogenous glucocorticoid administration (Table 2,3). A strong correlation has been found between prednisone maintenance doses above 5mg/d and a subnormal ACTH-stimulation test result. Hence, patients who are more likely to develop HPA axis suppression are those receiving high doses of glucocorticoids (>20-30mg hydrocortisone or equivalent) (Table 4) for a period longer than 3 weeks and patients who have developed overt Cushingoid features. In addition, the timing of drug administration may affect the degree of adrenal suppression. Thus, prednisolone in a dose of 5mg given at night before bedtime and 2.5mg in the morning will produce more marked HPA axis suppression compared to 2.5mg at night and 5mg in the morning. Higher evening doses block early morning ACTH surge whereas tissues sensitivity to glucocorticoids is increased in the evening and early night hours.

Table 2: Predictors of Glucocorticoid-Induced HPA Axis Suppression

Predictor	**Etiology/Risk of HPA Suppression**
Type of steroid and potency	Long-acting GCs lead to longer tissue life and longer suppression
Route of administration	Systemic GC therapy (parenterally): increased risk
Timing of administration	Decreased risk in alternate days scheme (from outset or converted before suppression); Increased risk: different doses scheme during day:
Duration and cumulative dose	Decreased risk in treatment ≤1week

Clinical features	Patients with Cushing's Syndrome: increased risk

HPA: hypothalamic-pituitary-adrenal; GC: glucocorticoid.

Table 3: Examples of Different Glucocorticoid-Induced HPA Axis Suppression
HC/cortisone acetate: least potent/suppressive; prednisone/prednisolone, methylprednisolone, triamcinolone: moderately suppressive; dexamethasone: strongest suppression
Topical GCs: increased risk but infants at increased risk; Inhaled GCs: increased risk versus oral/systemic GCs >risk children Fluticasone proprionate (ciclesonide: recent drug, decreased risk); Intraarticular GCs: transient suppression
Once-a-day dosing decreased risk intermediate/long acting GCs (prednisone/triamcinolone/dexamethasone); Short-acting HC/ cortisone acetate: twice-a-day (at waking 2/3; 5PM 1/3 total daily dose); evening doses suppress normal early morning ACTH surge leading to increased suppression, treat with single morning dose
"Short-term" 14 days course systemic GCs decreased risk

ACTH: adrenocorticotropin; HC: hydrocortisone; GC: glucocorticoid

Table 4: Glucocorticoid Equivalent Dose Compared to Cortisol	
	equivalent dose (mg)
Short-acting, low potency	
Cortisol	20
Cortisone	25
Intermediate-potency	
Prednisolone	5-7.5
Methylprednisolone	4
Long-acting, high potency	
Dexamethasone	0.75

Clinical awareness is crucial to identify patients with impending adrenal crisis. It is important to consider all patients with unexplained symptoms after glucocorticoid-withdrawal as candidates for possible AI and test them accordingly. An important feature that will raise suspicion of TAI (and SAI) besides drug history is the absence of skin pigmentation. Such patients have an intact renin-angiotensin-aldosterone system (RAAS) accounting for the differences in salt and water balance and clinical presentations compared to primary adrenal insufficiency.

Serum cortisol secretion at 08:00h if diagnostic tests are not feasible and until confirmatory testing is available can be considered a valuable screening method when AI is suspected. In patients with a low index of suspicion obtaining an 8AM cortisol and if the serum cortisol is > 15μg/dL, no further testing is needed. Similarly, a serum cortisol value <5 μg/dL suggests AI.

DIAGNOSTIC TESTS NEEDED TO DOCUMENT AI

Drug history and clinical features cannot be considered reliable tools for the evaluation of HPA axis function in patients treated with synthetic glucocorticoids. Several tests are commonly used in order to assess the degree of glucocorticoid-induced AI or HPA axis recovery (Table 5,6). Both the insulin tolerance test (ITT) and the metyrapone test have been employed as they are both highly sensitive. However, the risks involved with these tests do not justify their use compared to the rapid ACTH stimulation test or short synacthen test (SST) that can safely distinguish almost all cases of clinically significant adrenal suppression.

To evaluate the adequacy of HPA axis recovery, the SST is used to assess the capability of the adrenal cortex to respond to ACTH. However, because of the supraphysiologic ACTH levels achieved with the conventional SST (250 mcg of ACTH administered), if adrenal suppression is of recent onset, the adrenal gland may have not yet atrophied, and is still capable of responding to ACTH stimulation. In these cases, the low-dose SST (1 mcg of ACTH administered) has been proposed as an alternative as it results in lower plasma ACTH levels and thus less pronounced adrenal stimulation. It has recently been suggested that the low-dose SST is the best test to establish the diagnosis of SAI and TAI, whereas the high SST should be used for cases of primary AI. The use of salivary cortisol is also an effective alternative to serum cortisol when assessed in the high-dose ACTH test. Incremental cortisol response at the first SST was suggested as an important predictive factor of adrenal function recovery in SAI after exogenous glucocorticoid administration.

The CRH test can also be used in patients receiving glucocorticoids for prolonged periods, as it can assess both the ACTH and cortisol responses and can distinguish between SAI and TAI. In both conditions, cortisol concentrations are low at baseline and remain low after CRH administration. In patients with SAI, there is little or no ACTH response, whereas in patients with tertiary disease there is an exaggerated and prolonged response of ACTH, which is not followed by an appropriate cortisol response. On the contrary, patients with primary AI have high ACTH levels, which rise further following CRH while patients with hypothalamic disease show a steady rise in ACTH levels.

The prolonged ACTH stimulation test (depot or iv infusions 250μg cosyntropin over 8 hrs or over 24hrs) was suggested as a mean to differentiate between the different types of AI but is now rarely used in routine practice. In SAI or TAI, the adrenal glands display cortisol secretory capacity following prolonged stimulation with ACTH whereas in primary AI, they do not respond to ACTH being partially or completely destroyed.

In a recent systematic review of AI assessment after systemic glucocorticoid therapy, SST (conventional or low-dose) was the most frequently employed, but other tests were also used, including the insulin tolerance test (ITT, the “gold-standard”), the ACTH infusion, and the CRH tests.

Table 5: Diagnostic Tests Used to Diagnose Adrenal Insufficiency

Test / Sampling	Cortisol Response
Short Synacthen test 250mg iv or im cosyntropin; samples at 0/30’/60’	Physiologic response:>500-550nmol/L (18-20µg/dL)
Low-Dose Synacthen Test 1µg ACTH iv at 14:00: samples 10’ 15’ 20’ 25’ 30’ 35’ 40’ 45’	Physiologic response: >18 µg/dL (500nmol/L)
CRH stimulatory test iv bolus 1 or 100µg/kg or 100µgh-CRH/o-CRH	TAI: steady rise in ACTH not followed by appropriate cortisol response; SAI: no ACTH or cortisol response

ACTH: adrenocorticopic hormone; CRH: corticotropin-releasing hormone; im: intramuscular; iv: intravenous; PAI: primary adrenal insufficiency; SAI: secondary adrenal insufficiency; TAI: tertiary adrenal insufficiency

Table 6: Diagnostic Tests Not Commonly Used to Diagnose and Differentiate Adrenal Insufficiency

Test / Sampling	Cortisol Response
Prolonged ACTH stimulation test Depot or iv infusions 250µg cosyntropin over 8hrs(**A**): cortisol/24hr urinary cortisol/17OHCS before and after infusion or over 24hrs on 2(or3) consecutive days(**B**)	Physiologic response: **A**:24hr urinary 17-OHCS excretion increase 3-5-fold; serum cortisol>20µg/dL (550nmol/L) at 30’ and 60’; >25µg/dL (690 nmol/L) at 6-8hrs post-initiation infusion; **B:** at 4hrs >1000nmol/L (36µg/dL) beyond this time, no further increase; SAI: delayed response at 24 and 48hrs than 4hrs; PAI no response at either time
ITT iv insulin (0.1-0.15U/kg); Samples 0 30’45’ 60’90’120’ with adequate clinical and biochemical hypoglycemia	Physiologic response: >500nmol/L (18µg/dL)
overnight metyrapone test 30 mg/kg (max 3g)	Physiologic response: Increased ACTH plus peak 11-

at midnight; cortisol/ 11-deoxycortisol measured at 8.00h the following morning	deoxycortisol >7 mg/dL.

ACTH: adrenocorticopic hormone; iv: intravenous; ITT: insulin tolerance test, PAI: primary adrenal insufficiency; SAI: secondary adrenal insufficiency; SST: short synacthen test; 17OHCS: 17-hydroxycorticoids, TAI: tertiary adrenal insufficiency

THERAPY

Glucocorticoid withdrawal is indicated when the use of the steroid is no longer needed or when significant side effects develop. The suggested method of glucocorticoid withdrawal is dose tapering to avoid the occurrence of AI.

Adrenal insufficiency is a potentially life-threatening medical emergency when presenting as adrenal crisis, which requires prompt treatment with hydrocortisone and fluid replacement. Once, clinically suspected, treatment should be initiated and not be delayed while waiting for definitive proof of diagnosis. Blood samples should be obtained for measurement of cortisol concentrations later, and the management approach should be similar to the resuscitation of any critically ill patient.

There is currently no consensus regarding rapid or slow tapering of glucocorticoids and exacerbation and/or relapse rates of the underlying diseases. The key action is that glucocorticoid withdrawal should not be abrupt. In clinical practice, patients being on any steroid dose for less than 2 weeks are not likely to develop adrenal suppression and are advised to stop therapy without tapering. The possible exception to this is the patient who receives frequent "short" steroid courses, as in asthma treatment. In longer regimens, the objective is to rapidly reduce the therapeutic dose to a physiologic level of cortisol (equivalent to 10-15 mg/ms/d) (Table 7). However, a recent systematic review of 73 studies demonstrated evidence of AI following low doses and short durations of glucocorticoid administration at less than 5 mg prednisolone equivalent dose/day, less than 4 weeks of exposure, cumulative dose less than 0.5 g, and following tapered withdrawal.

Table 7: Tapering After a Long-Term Glucocorticoid Regimen	
1. Reduction by 2.5mg prednisolone or equivalent	every 3-4 days over few weeks
2. Slower withdrawal	until physiological level achieved (5-7.5mg of prednisolone)
3a. Decrease by 1mg/d prednisolone or equivalent	every 2-4weeks (depending patient's general condition) until medication cessation
Or	
3b. Switch to 20mg/d HC+ Decrease by 2.5mg/d	every week until the dose: 10mg/d
4. After 2-3months on same dose	SST or ITT

5a. Pass Response	discontinuation of GC
Or	
5b. No HPA axis recovery	Treatment continuation+re-assessment

GC: glucocorticoid; ITT: insulin tolerance test; SST: short synacthen dose

Other tapering regimens suggest switching the patient to an alternate day administration of intermediate action glucocorticoids before cessation of treatment. Irrespectively of the tapering regimen used, if a glucocorticoid withdrawal syndrome, AI or exacerbation of the underlying disease develops, the dose being given at the specific time should be increased or maintained longer. Recent systematic reviews implied that the evidence for the tapering regimens used nowadays is not robust, despite the fact that rapid reduction to a physiologic glucocorticoid dose (5-7.5 mg prednisolone daily or equivalent), and the slow reduction thereafter, is the most frequently used regimen for clinicians.

Care should be given during the tapering regimens period on the interpretation of laboratory tests for cortisol levels measurement. The steroid dose before the test should be omitted (hold off evening and morning dose for hydrocortisone or prednisolone, longer for the other synthetic glucocorticoids); if serum cortisol secretion at 08:00h is > 15μg/dL, the tapering regimen changes to a rapid tapering off of exogenous glucocorticoids. Moreover, there are conditions that affect cortisol-binding globulin concentration (CBG) (↓: inflammation, nephrotic syndrome, liver disease, immediate postoperative period or requiring intensive care, rare genetic disorders; ↑: estrogen, pregnancy, mitotane). Systemic estrogens should be discontinued at least for 4 weeks prior to testing; estrogen patches are preferred since they do not affect CBG. Different criteria may apply according to the cortisol assay.

FOLLOW-UP

Since, there is evidence that AI may persist in 15% of patientsfor more than 3 years after glucocorticoid withdrawal, careful monitoring of patients and gradual glucocorticoid withdrawal should always be performed to avoid manifestations of adrenal suppression and/or an adrenal crisis or reactivation of the underlying disease. In general, plasma ACTH concentrations are not helpful in estimating the optimal glucocorticoid dose whereas mineralocorticoid replacement is not required. All patients treated with glucocorticoids long-term should receive detailed instructions for glucocortiocoid supplementation equivalent to 100-150mg of hydrocortisone during major stresses (surgery, fractures, severe systemic infections, major burns) until their HPA axis fully recovers and to carry means of identification (medical alert bracelet).

Since full HPA axis recovery may take as long as one year or even longer, abrupt cessation of glucocorticoid treatment or quick tapering can precipitate an acute AI crisis. The diagnosis is a medical emergency, and treatment should be the immediate administration of fluids, electrolytes, glucose, and parenteral glucocorticoids.

GUIDELINE

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