REVIEW

CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will anticipate hyperglycemia and adrenal suppression in patients on long-term glucocorticoid therapy and manage these problems effectively

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Glucocorticoid-induced diabetes and adrenal suppression: How to detect and manage them

ABSTRACT

Glucocorticoids, commonly used to treat multiple inflammatory processes, can cause hyperglycemia, Cushing syndrome, adrenal suppression, and, when they are discontinued, adrenal insufficiency. Physicians must be aware of these adverse effects and be equipped to manage them.

KEY POINTS

Nonfasting plasma glucose levels are more sensitive than fasting levels for detecting glucocorticoid-induced diabetes, and antidiabetic agents that have greater effects on random postprandial plasma glucose levels are more suitable than those that mostly affect fasting levels.

Even those glucocorticoid formulations that are not intended to have systemic effects (eg, eye drops, inhaled corticosteroids, creams, intra-articular injections) can cause adrenal suppression and, therefore, if they are discontinued, steroid withdrawal and adrenal insufficiency.

Needed are studies comparing antidiabetic regimens for glucocorticoid-induced hyperglycemia and studies comparing glucocorticoid tapering schedules for adrenal suppression to determine the best way to manage these adverse effects.

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Glucocorticoids are commonly prescribed by primary care physicians and specialists alike for multiple medical problems, acute as well as chronic.

However, these useful drugs have adverse effects on multiple endocrine systems, effects that include diabetes (or worsening of hyperglycemia in those with known diabetes), Cushing syndrome, adrenal suppression, osteoporosis (reviewed in the *Cleveland Clinic Journal of Medicine* in August 2010),[1] and dyslipidemia. In addition, suppression of gonadotropins, growth hormone, and, acutely, thyrotropin can ensue.

The focus of this review is on the diabetogenic and adrenal suppressive effects of glucocorticoids and their management. We describe the rationale for choosing specific drugs to counter hyperglycemia, tests for determining adrenal suppression and systemic glucocorticoid absorption, and how and why to taper these drugs.

WIDELY USED DRUGS

Although glucocorticoids (often simply called steroids or corticosteroids, although not all steroids are corticosteroids, and not all corticosteroids are glucocorticoids) are the core treatment for adrenal insufficiency, in most cases they are prescribed for their anti-inflammatory effects. They act through multiple pathways at the cellular and molecular levels, suppressing the cascades that would otherwise result in inflammation and promoting pathways that produce anti-inflammatory proteins.[2]

In addition to formulations that are intended to have systemic effects, other, "local" formulations are made for specific conditions, such as intra-articular injections for arthritis, epidural injections for lumbar disk pain, eye drops for uveitis, nasal sprays for allergic rhinitis, inhalers for asthma, and topical ointments and creams for eczema. However, as we will discuss, even these preparations can have systemic effects.

GLUCOCORTICOID-INDUCED DIABETES IS COMMON

Glucocorticoids are the most common cause of drug-induced diabetes. Though the exact prevalence is not known, a few observations suggest that glucocorticoid-induced diabetes or hyperglycemia is common:

- In patients with rheumatoid arthritis, mean age 62 years, nearly 9% developed diabetes in the 2 years after starting glucocorticoid treatment, which was a higher rate than expected.[3]
- In nondiabetic patients with primary renal disease treated with prednisolone 0.75 mg/kg/day, 42% were found to have 2-hour post-lunch plasma glucose concentrations higher than 200 mg/dL but normal fasting glucose levels.[4]
- In a case-control study, the odds ratio of starting an oral hypoglycemic agent or insulin was 1.77 for patients receiving a hydrocortisone-equivalent dose of 1 to 39 mg/day, 3.02 for 40 to 79 mg/day, 5.82 for 80 to 119 mg/day, and 10.34 for 120 mg/day or more.[5] (For a full discussion of glucocorticoid equivalents, see the section below on Cushing syndrome and adrenal suppression.)
- In patients with type 1 diabetes, prednisone 60 mg/day raised the blood glucose levels starting 6 hours after the prednisone dose.[6]
- Diabetic ketoacidosis and hyperosmolar nonketotic syndrome have been reported as a result of glucocorticoid treatment.[7–9]

GLUCOCORTICOIDS CAUSE DIABETES MAINLY VIA INSULIN RESISTANCE

The mechanism by which glucocorticoids cause diabetes predominantly involves insulin resistance rather than decreased insulin production. In fact, in a study in healthy volunteers,[10] hydrocortisone infusion resulted in higher insulin production than saline infusion did. (In high doses, however, glucocorticoids have been shown to decrease insulin secretion.[11])

Normally, in response to insulin, the liver decreases its output of glucose. Glucocorticoids decrease the liver's sensitivity to insulin, thereby increasing hepatic glucose output.[12] They also inhibit glucose uptake in muscle and fat, reducing insulin sensitivity as much as 60% in healthy volunteers. This seems primarily due to a postreceptor effect, ie, inhibition of glucose transport.[13–15]

THE PEAK EFFECT OCCURS 4 TO 6 HOURS AFTER DOSING

To understand the optimal time for checking plasma glucose and to apply appropriate treatment, we should consider the pharmacokinetic profile of glucocorticoids.

Studied using the whole-blood lymphocyte proliferation technique, prednisone shows a peak effect at about 4 to 6 hours and a duration of action of 13 to 16 hours.[16] This closely resembles what we see in terms of glucose excursion with this drug.[17] Two studies of intravenous dexamethasone 10 mg showed that glucose levels rose within 4 hours of injection, but did not pursue this beyond that time frame.[18,19]

Glucocorticoids are the most common cause of drug-induced diabetes

PATIENTS WITHOUT A PREVIOUS DIAGNOSIS OF DIABETES

Be alert for new-onset diabetes

For most diseases treated with glucocorticoids, clinicians can estimate in advance how long the patient will need to take the drug. We can arbitrarily classify the projected exposure as either short-term (3 to 4 weeks or less, such as a 6-day course of methylprednisolone for allergic conditions) or long-term (such as in transplant recipients to prevent rejection or to treat graft-vs-host disease). Hyperglycemia is a potential concern with both short-term and long-term treatment. However, guidelines on checking blood sugar levels, as opposed to relying on symptoms alone, are available only for long-term glucocorticoid treatment.

TABLE 1

Proposed methods of detecting glucocorticoid-induced diabetes

More sensitive

Random plasma glucose (preferably in the afternoon or 2 hours after a meal) ≥ 200 mg/dL with classic symptoms of hyperglycemia

75-g oral glucose tolerance test, 2-hour value ≥ 200 mg/dL

Less sensitive but more feasible*

Fasting plasma glucose ≥ 126 mg/dL

Hemoglobin A_{1c} ≥ 6.5%

The American Diabetes Association recommends that, for a diagnosis of diabetes, results should be confirmed with repeat testing in the absence of unequivocal hyperglycemia.[21]

*May be more useful in patients with preexisting prediabetes or risk factors for diabetes, or twice-daily glucocorticoid dosing

Patients should be warned about diabetes symptoms when starting glucocorticoid treatment

Patients beginning treatment should be warned of typical diabetes symptoms such as thirst and increased urination and, should these occur, to seek medical attention to have their blood glucose level checked. It is also reasonable to have them return in a week for a random postprandial plasma glucose test in the mid-afternoon.

Why this timing? In most once-daily regimens, glucocorticoids are given in the morning to prevent adrenal suppression (discussed below). In our experience, glucose levels start to rise mid-morning and continue to increase until bedtime. Measuring glucose levels 1 to 2 hours after lunch allows for both the glucocorticoid action and the carbohydrate absorption from lunch to reach their peaks. If hyperglycemia is going to happen, it should be detectable by then. A glucose level of 200 mg/dL or higher should prompt the practitioner to pursue this further.

If glucocorticoid treatment is to continue beyond 3 to 4 weeks, the only population for which there are published guidelines on managing glucocorticoid-related diabetes is transplant recipients. International consensus guidelines, published in 2003, suggest checking the fasting plasma glucose level once a week for the first 4 weeks after transplantation, then at 3 months, at 6 months, and then once a year.[20]

Though practical, this suggestion does not reflect the fact that glucocorticoids often do not affect fasting plasma glucose, especially if given once daily in the morning at doses of 30 mg or less of prednisone or its equivalent. These guidelines thus may not be applicable to other populations with glucocorticoid-induced diabetes.

The transplant guidelines do mention that an oral glucose tolerance test may be more sensitive, but this is often cumbersome to perform. We believe that checking random postprandial plasma glucose levels is helpful in this regard.

The American Diabetes Association cutoff for diagnosing diabetes when using a random (ie, nonfasting) plasma glucose level is 200 mg/dL or higher in a patient with classic symptoms of hyperglycemia such as polyuria and polydipsia (**TABLE 1**).[21] In the absence of such symptoms, a hemoglobin A_{1c}, fasting plasma glucose, or oral glucose tolerance test may be used and the results confirmed with repeat testing.

If the patient was at risk of developing diabetes even before receiving a glucocorticoid (for example, if he or she is overweight, has a family history of diabetes, or had a previous hemoglobin A_{1c} of 5.7% or higher), then a fasting plasma glucose level of 126 mg/dL or higher or a hemoglobin A_{1c} of 6.5% or higher might suffice to diagnose diabetes. Results should be confirmed on a separate day in the absence of unequivocal hyperglycemia. Fasting hyperglycemia can also be seen in patients receiving higher once-daily glucocorticoid doses—in our experience, an equivalent of prednisone 40 mg once a day in the morning—or twice-daily dosing.

A hemoglobin A_{1c} checked less than 2 to 3 months after starting glucocorticoid treatment will not be sensitive in picking up glucocorticoid-induced diabetes if the patient did not have underlying diabetes.

Diet and exercise may not be practical

Though diet and exercise are important in managing diabetes, the condition for which the patient is receiving a glucocorticoid may prevent him or her from exercising, at least in the acute phase of the illness.

In addition, though the exact mechanism is not known, glucocorticoids increase hunger, and so decreasing food intake is not easy either. Nonetheless, patients should be familiarized with what carbohydrates are and should be advised to reduce their intake of them.

For suspected type 1 diabetes, start insulin

If type 1 diabetes is suspected, for example, in patients who are lean, younger than 30 years, or who had presented with diabetic ketoacidosis, then insulin should be started. In equivocal cases, insulin therapy can commence while testing is done for C-peptide, glutamic acid decarboxylase antibodies, islet cell antibodies, and insulinoma-associated protein antibodies.

For all other patients, keep in mind the characteristics of glucocorticoids (TABLE 2) that may affect the drug treatment of diabetes.

Starting oral antidiabetic drugs

Some patients may have contraindications to specific drugs. For example, metformin (Glucophage) is contraindicated if the serum creatinine level is elevated, an abnormality that renal transplant patients may continue to have.

If the patient has no such contraindications, we have found the following medications suitable in view of their efficacy, low risk of hypoglycemia, or lack of distressing side effects. They will often lower glucose levels enough to achieve capillary blood glucose or fingerstick goals (discussed below). None of them has been specifically approved by the US Food and Drug Administration for glucocorticoid-induced diabetes, but they are approved for type 2 diabetes.

Guidelines from the American Association of Clinical Endocrinologists for type 2 diabetes call for starting monotherapy if the hemoglobin A_{1c} is 6.5% to 7.5%, dual therapy if it is 7.6% to 9%, triple therapy if it is higher than 9% and the patient has no symptoms, and insulin if it is higher than 9% and the patient does have symptoms.[22]

In terms of estimated average glucose levels, these categories correspond to 140 to 169 mg/dL for monotherapy, 171 to 212 mg/dL for dual therapy, and higher than 212 mg/dL for triple therapy or insulin. Since estimated average levels also include fasting glucose levels (which are lower in glucocorticoid-induced diabetes compared with nonfasting levels), and because we use the American Diabetes Association general hemoglobin A_{1c} goal of less than 7%, we believe that our suggestions below are reasonable.

We divide our recommendations according to initial random (ideally, 1- to 2-hour postprandial) plasma glucose levels.

TABLE 2

Treating glucocorticoid-induced diabetes: Things to keep in mind

Glucocorticoids cause hunger, weight gain, and edema

Oral glucocorticoids are often given in the morning to mimic the diurnal rhythm of cortisol

Glucocorticoids given in the morning affect plasma glucose levels later in the day rather than fasting plasma glucose

Higher glucocorticoid doses or twice-daily dosing can also increase fasting plasma glucose levels

Chronic glucocorticoid administration is often followed by a taper

If the random or 1- to 2-hour post-meal plasma glucose is lower than 220 mg/dL

In this situation the choices are:

- Metformin
- Dipeptidyl peptidase-4 (DPP-4) inhibitors ("gliptins")
- Meglitinides ("glinides"). The guidelines on new-onset diabetes after transplantation point out that meglitinides may be the safest agents apart from insulin in the renal transplant population, but does acknowledge that efficacies of different oral agents have not been compared in this group.[20]
- Glucagon-like protein-1 (GLP-1) agonists
- Sulfonylureas. However, the longer-acting forms such as glimepiride (Amaryl) are not suitable if the fasting plasma glucose is not affected.

We have not used thiazolidinediones ("glitazones") routinely because they can cause weight gain and edema—problems that are already seen with the use of steroids—and have a slower onset of action.

Metformin is contraindicated if the serum creatinine is elevated

If the random or 1- to 2-hour post-meal plasma glucose is 220 to 300 mg/dL

Often, a combination of drugs or insulin (see below) is needed. However, you can start with one agent and add a second agent within 2 or 3 months (as is recommended for type 2 diabetes).[22,23] The following combinations of the agents listed above are supported by published guidelines for type 2 diabetes:

- Metformin plus a sulfonylurea[22,23]
- Metformin plus a glinide[22]
- Metformin plus a GLP-1 agonist[23]
- Metformin plus a DPP-4 inhibitor.[22]

If the random or 1- to 2-hour post-meal plasma glucose is higher than 300 mg/dL

In our experience, if their plasma glucose levels are this high, patients are experiencing frank symptoms of hyperglycemia.

Insulin addresses those symptoms and avoids the prolonged wait that often results from unsuccessfully starting one agent and then adding another. Of all the available drugs, insulin is the only one that can be used despite multiple underlying illnesses; it does not cause a lot of drug interactions, and the dose can be adjusted upward and downward in increments to fit the patient's needs, especially when a larger glucocorticoid load is given up front and then is tapered either slowly or rapidly. However, it can cause hypoglycemia and weight gain.

A starting total daily insulin dose of 0.15–0.3 U/kg is reasonable

The initial total daily dose of insulin can be based on the patient's weight. A starting total daily dose of 0.15 to 0.3 U/kg is reasonable—on the lower end if only the postprandial glucose levels are elevated, and on the higher end if both fasting and postprandial glucose levels are affected.

If fasting glucose levels are not elevated, then Neutral Protamine Hagedorn insulin (which is intermediate-acting) or a premixed combination of an intermediate-acting plus a fast- or short-acting insulin can be given once a day before breakfast, or even before lunch if the glucose levels start to rise only after lunch.

If both the fasting and the postprandial glucose levels are elevated, regimens similar to those for type 1 or insulin-requiring type 2 diabetes can be used, except that the ratios of the doses are tilted more toward covering postprandial than fasting hyperglycemia:

- Long-acting insulin plus prandial insulin, in a ratio of 30:70 to 50:50. As glucocorticoids are tapered, the long-acting insulin may have to be discontinued while the prandial doses are continued, since the fasting glucose level decreases first.
- Premixed insulins, with one-half to two-thirds of the dose given before breakfast and the rest before the evening meal, with the possibility of a third injection before lunch. As glucocorticoids are tapered, the evening dose is tapered first.
- Intermediate-acting insulin plus short- or fast-acting insulin in the morning (these two will make up one-half to two-thirds of the total daily dose), short- or fast-acting insulin before the evening meal, and intermediate-acting insulin at bedtime. As glucocorticoids are tapered, the bedtime insulin is tapered first.

Capillary blood glucose (fingerstick) checks

The timing and frequency of fingerstick checks depend on the treatment.

Though postprandial testing is ideal, it is often not practical or convenient. Before lunch, before dinner, and at bedtime are good alternatives since they reflect the pattern of glucose rise throughout the day. For patients on diet and exercise with or without agents other than insulin, testing once or twice a day is reasonable, rotating times before meals (including fasting if this time is affected) and at bedtime.

For patients on insulin, checking two to four times a day initially would help match insulin doses with glucose excursions. For continued care, the American Diabetes Association recommends fingerstick checks three times daily in patients on multiple insulin injections, but it has no specific recommendations for those on once-a-day insulin.[21] We have been recommending that our patients on once-daily insulin check at least twice a day.

Goal fingerstick glucose levels that we use are in accordance with the American Diabetes Association guidelines for diabetes in general[21]:

- Before meals 70 to 130 mg/dL *or*
- 1 to 2 hours after meals < 180 mg/dL.

During steroid taper, if the glucocorticoid dose is in the lower range (eg, a prednisone-

equivalent dose of approximately 7.5 mg per day or less), the fingerstick glucose levels are at the lower end of the target range, and the patient is on a single antidiabetic agent that does not often cause hypoglycemia (eg, metformin), then it is reasonable to ask the patient to not take the antidiabetic medication for 3 to 7 days while continuing to check fingersticks to see if it needs to be resumed. Patients on agents that can cause hypoglycemia need to check more often during the 1 to 3 days after the glucocorticoid dose reduction, as it may take this much time for the glycemic effect to diminish and to adjust the diabetes medication to the appropriate dose.

STARTING GLUCOCORTICOIDS IN PATIENTS WITH KNOWN DIABETES

Fingerstick checks more often

Most patients will already have a glucose meter. They should be instructed to check as discussed above if they do not have a previous diagnosis of diabetes, or to continue as they are doing if they are already checking more often. Patients who have been checking only fasting levels should be instructed to check later in the day, either before or 1 to 2 hours after meals, as discussed above. Patients on oral medications may need additional oral agents or insulin.

Adjust medications if glucose is not at goal

Patients with type 2 diabetes treated with diet and exercise alone can be started on the medications discussed above if their fingerstick readings are not at goal.

If they are already on insulin, we advise them to increase the short- or fast-acting insulins and the morning intermediate-acting insulin by at least 10% to 20% as soon as an elevation in glucose is detected. Long-acting insulin or nighttime intermediate-acting insulin should be increased if fasting glucose levels are affected.

Insulin requirements can double depending on the glucocorticoid dose. In patients with type 1 diabetes who were given prednisone 60 mg orally for 3 days, mean blood glucose levels increased from a baseline of 110 mg/dL at baseline to 149 mg/dL on the days on prednisone.[6] The average blood glucose level remained elevated at 141 mg/dL on the day after the last dose of prednisone. The insulin dose increased by 31% to 102% (mean 69%).

CUSHING SYNDROME AND ADRENAL SUPPRESSION

Unlike glucocorticoid-induced diabetes, in which the dilemma is often when to initiate antidiabetic treatment, the question for patients in whom Cushing syndrome or adrenal suppression has developed is when to discontinue glucocorticoids.

Adrenal suppression for the most part goes hand in hand with exogenous Cushing syndrome. If cushingoid features develop, we can infer that the dose of exogenous glucocorticoid exceeds the physiologic needs. This supraphysiologic dosing also leads to suppression of endogenous cortisol production. The suppression occurs at the level of the hypothalamus and pituitary gland, with subsequent atrophy of the part of the adrenal cortex that produces endogenous glucocorticoids.

To understand further the concept of supraphysiologic dosing, the following interconversion of systemic glucocorticoid effects is helpful[24,25]:

hydrocortisone 20 mg ≈
prednisone or prenisolone 5 mg ≈
dexamethasone 0.75 mg.

We recommend that patients on once-daily insulin check their glucose at least twice a day

However, there is not much information on interconversion for the local preparations (intra-articular, epidural, inhaled, topical).

Moreover, the definition of supraphysiologic dosing seems to be evolving. Though a total hydrocortisone-equivalent dose of 30 mg/day is still often touted as physiologic replacement, many patients require less. Several studies in the early 1990s, mostly in children and adolescents, showed the mean daily cortisol production rate to be 4.8 to 6.8 mg/m^2/day, or closer to 10 to 15 mg/day.[26–28] For purposes of this discussion, a physiologic dose will be defined as up to 30 mg hydrocortisone per day or its equivalent.

Adrenal suppression vs insufficiency

Adrenal suppression is often confused with adrenal insufficiency.

Adrenal suppression occurs when cortisol production is decreased because of the presence of exogenous glucocorticoids or other

drugs, such as megestrol acetate (Megace), that act on the glucocorticoid receptor. Another situation beyond the scope of this review is excess endogenous cortisol production by an adrenal adenoma or adrenal carcinoma that causes suppression of the contralateral adrenal gland.[29]

In contrast, adrenal insufficiency is caused by failure of the adrenal gland to produce cortisol as a result of an innate disorder of the adrenal gland (eg, Addison disease) or pituitary gland (eg, pituitary surgery).

Hence, endogenous cortisol production in a patient taking supraphysiologic doses of exogenous glucocorticoids may be suppressed. Recovery of endogenous cortisol production is expected after stopping the exogenous glucocorticoid, though the time to recovery can vary and the patient can be adrenally insufficient if the glucocorticoid is stopped abruptly.

In addition, during times of intercurrent illness, a patient with adrenal suppression may be relatively adrenally insufficient and may need larger doses ("stress doses") of glucocorticoids, since the adrenal glands may be unable to mount a stress response.[29]

Insulin requirements can double, depending on the glucocorticoid dose

Local steroids can suppress the adrenal glands

Glucocorticoids are the most common cause of Cushing syndrome. Oral formulations such as dexamethasone, prednisone, and hydrocortisone taken in supraphysiologic doses and for prolonged durations are easily recognized as obvious causes of Cushing syndrome. However, intra-articular, epidural, inhaled, nasal, ocular, and topical steroids—so-called local preparations—have also been linked to Cushing syndrome, and physicians are less likely to recognize them as causes.[30–38]

In a study in 16 pediatric patients with asthma and 48 controls, inhaled beclomethasone dipropionate (Qvar) 300 to 500 µg daily resulted in adrenal suppression in 100% of patients after 6 to 42 months, as determined by an insulin tolerance test.[30]

The topical steroid betamethasone (Diprosone) carries a warning that systemic absorption of topical steroids can cause adrenal suppression.[39] Intra-articular, intranasal, epidural, and ocular routes are also reported to cause adrenal suppression.[32–38]

When is adrenal suppression more likely?

Adrenal suppression is more likely in the following situations:

- Longer duration of treatment. Studies have shown that exposure to supraphysiologic steroid doses for 2 weeks or less might already suppress the adrenal glands, but the clinical significance of this is unclear since some recovery already occurs a few days after the glucocorticoids are discontinued.[31,40]
- Supraphysiologic doses, stronger formulations, longer-acting formulations.[41]

When is adrenal suppression less likely?

Adrenal suppression is less likely in the following situations:

- Regimens that mimic the diurnal rhythm of cortisol (higher dose in the morning, lower dose in the afternoon)[42]
- Alternate-day dosing of steroids.[43]

Steroid withdrawal vs adrenal insufficiency

Another phenomenon that can be confused with adrenal insufficiency or glucocorticoid insufficiency is steroid withdrawal, in which patients experience lethargy, muscle aches, nausea, vomiting, and postural hypotension as glucocorticoids are tapered and their effects wane.[42] Increasing the glucocorticoid dose for presumed adrenal insufficiency may delay recovery of the adrenal function and would have to be weighed against the patient's symptoms.

The following may help distinguish the two: if the patient is on supraphysiologic glucocorticoid doses, then he or she is not glucocorticoid-deficient and is likely suffering from steroid withdrawal. At this point, patients may just need reassurance, symptomatic treatment, or if necessary, a brief (1-week) increase of the previous lowest dose, followed by reevaluation.

With local glucocorticoid preparations that may be systemically absorbed, however, there is no good way of estimating dose equivalence. In these situations, the decision to simply reassure the patient or give symptomatic treatment—as opposed to giving low-dose oral glucocorticoids such as hydrocortisone 5 to 10 mg daily for a week followed by reevaluation—depends on the severity of symptoms and whether the patient has quick access to medical attention should he or she develop an intercurrent illness.

Identifying patients at risk of adrenal suppression

Patients presenting with weight gain or symptoms suggesting Cushing syndrome should be asked about steroid intake and should be prompted to recall possible nonoral routes. In addition, patients presenting with muscle aches and fatigue—symptoms of steroid withdrawal—may have received unrecognized local glucocorticoids that were systemically absorbed, now with diminishing effects.

The ACTH stimulation test for adrenal recovery

Testing can be done to see if the adrenal glands have recovered and glucocorticoid therapy can be discontinued (see **TAPERING FROM GLUCOCORTICOIDS,** below).

The test most often used is the corticotropin (ACTH) stimulation test. Since the suppression is at the level of the hypothalamus and the pituitary gland, the ACTH stimulation test is an indirect method of assessing hypothalamic and pituitary function in the context of glucocorticoid-induced adrenal suppression. It has good correlation with the insulin tolerance test, the gold-standard test for an intact hypothalamic-pituitary-adrenal axis.

The synthetic ACTH cosyntropin (Cortrosyn) 250 µg is injected intravenously or intramuscularly, and a cortisol level is drawn at baseline and 30 and 60 minutes later. Other doses such as 1 µg or 10 µg have been reported but are not yet widely accepted. A cortisol level of greater than 18 to 20 µg/dL at any time point shows that the adrenals have regained function and the steroids may be discontinued.[42] If adrenal suppression persists, weaning from steroids should continue.

In reality, it may not be possible or practical to do an ACTH stimulation test, as not all physicians' offices have a supply of cosyntropin or the manpower to perform the test correctly. In these cases, weaning can progress with monitoring of symptoms.

Testing for synthetic glucocorticoids in the urine and serum can demonstrate systemic absorption and may be helpful in patients who do not recall receiving steroids.[33]

Tapering from glucocorticoids

Several tapering schedules have been suggested (although not necessarily validated). Whether and how to taper depend on how long the glucocorticoid has been taken.

If taken for less than 1 week, glucocorticoids can be stopped without tapering, regardless of the dose.

If taken for 1 to 3 weeks, the decision to taper depends on the clinician's assessment of the patient's general health or constitution and the illness for which the glucocorticoid was prescribed. For example, if the underlying disease is less likely to flare with a gradual dose reduction, then tapering would be suitable.[44]

If taken for more than 3 weeks, the practice has been a more rapid taper at the beginning until a physiologic dose is reached. How quickly to reduce the dose depends on whether the underlying illness is expected to flare up, or if the patient might experience steroid withdrawal symptoms.

One schedule is to lower the glucocorticoid dose by an amount equivalent to prednisolone 2.5 mg every 3 to 4 days when above the physiologic dose, then to taper more slowly by 1 mg every 2 to 4 weeks.[44] Once the physiologic dose is reached, one can switch to the equivalent dose of hydrocortisone and decrease the dose by 2.5 mg a week until a daily dose of 10 mg a day is reached and maintained for 2 to 3 months, and then perform a test of adrenal function (see above).[44] Passing the test implies that the adrenal glands have recovered and the glucocorticoid can be stopped.

Even 'local' steroids can cause Cushing syndrome

Another option is to switch to alternate-day therapy once a physiologic dose is reached and to test 8:00 AM cortisol levels, continuing the glucocorticoid and retesting in 4 to 6 weeks if the value is less than 3 µg/dL; stopping the glucocorticoid if the value is higher than 20 µg/dL; and performing an ACTH stimulation test for values in between.[45]

A review of other tapering regimens for chronic diseases, mostly pulmonary, did not find enough evidence to recommend one particular schedule over another.[46] The tapering schedule may have to be adjusted to prevent disease flare and symptoms of steroid withdrawal.

Locally administered steroids. Since the equivalence of systemically absorbed local glucocorticoids is not known, these patients are likely to present when they have symptoms of steroid withdrawal. In this situation, testing adrenal function will help. ■

REFERENCES

1. **Dore RK**. How to prevent glucocorticoid-induced osteoporosis. Cleve Clin J Med 2010; 77:529–536.
2. **Rhen T, Cidlowski JA**. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. N Engl J Med 2005; 353:1711–1723.
3. **Panthakalam S, Bhatnagar D, Klimiuk P**. The prevalence and management of hyperglycaemia in patients with rheumatoid arthritis on corticosteroid therapy. Scott Med J 2004; 49:139–141.
4. **Uzu T, Harada T, Sakaguchi M, et al**. Glucocorticoid-induced diabetes mellitus: prevalence and risk factors in primary renal diseases. Nephron Clin Pract 2007; 105:c54–c57.
5. **Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J**. Glucocorticoids and the risk for initiation of hypoglycemic therapy. Arch Intern Med 1994; 154:97–101.
6. **Bevier WC, Zisser HC, Jovanovic L, et al**. Use of continuous glucose monitoring to estimate insulin requirements in patients with type 1 diabetes mellitus during a short course of prednisone. J Diabetes Sci Technol 2008; 2:578–583.
7. **Cagdas DN, Paç FA, Cakal E**. Glucocorticoid-induced diabetic ketoacidosis in acute rheumatic fever. J Cardiovasc Pharmacol Ther 2008; 13:298–300.
8. **Bedalov A, Balasubramanyam A**. Glucocorticoid-induced ketoacidosis in gestational diabetes: sequela of the acute treatment of preterm labor. A case report. Diabetes Care 1997; 20:922–924.
9. **Yang JY, Cui XL, He XJ**. Non-ketotic hyperosmolar coma complicating steroid treatment in childhood nephrosis. Pediatr Nephrol 1995; 9:621–622.
10. **Nielsen MF, Caumo A, Chandramouli V, et al**. Impaired basal glucose effectiveness but unaltered fasting glucose release and gluconeogenesis during short-term hypercortisolemia in healthy subjects. Am J Physiol Endocrinol Metab 2004; 286:E102–E110.
11. **Matsumoto K, Yamasaki H, Akazawa S, et al**. High-dose but not low-dose dexamethasone impairs glucose tolerance by inducing compensatory failure of pancreatic beta-cells in normal men. J Clin Endocrinol Metab 1996; 81:2621–2626.
12. **Rizza RA, Mandarino LJ, Gerich JE**. Cortisol-induced insulin resistance in man: impaired suppression of glucose production and stimulation of glucose utilization due to a postreceptor detect of insulin action. J Clin Endocrinol Metab 1982; 54:131–138.
13. **Meyuhas O, Reshef L, Gunn JM, Hanson RW, Ballard FJ**. Regulation of phosphoenolpyruvate carboxykinase (GTP) in adipose tissue in vivo by glucocorticoids and insulin. Biochem J 1976; 158:1–7.
14. **Tappy L, Randin D, Vollenweider P, et al**. Mechanisms of dexamethasone-induced insulin resistance in healthy humans. J Clin Endocrinol Metab 1994; 79:1063–1069.
15. **Pagano G, Cavallo-Perin P, Cassader M, et al**. An in vivo and in vitro study of the mechanism of prednisone-induced insulin resistance in healthy subjects. J Clin Invest 1983; 72:1814–1820.
16. **Magee MH, Blum RA, Lates CD, Jusko WJ**. Pharmacokinetic/pharmacodynamic model for prednisolone inhibition of whole blood lymphocyte proliferation. Br J Clin Pharmacol 2002; 53:474–484.
17. **Burt MG, Roberts GW, Aguilar-Loza NR, Frith P, Stranks SN**. Continuous monitoring of circadian glycemic patterns in patients receiving prednisolone for COPD. J Clin Endocrinol Metab 2011; 96:1789–1796.
18. **Hans P, Vanthuyne A, Dewandre PY, Brichant JF, Bonhomme V**. Blood glucose concentration profile after 10 mg dexamethasone in non-diabetic and type 2 diabetic patients undergoing abdominal surgery. Br J Anaesth 2006; 97:164–170.
19. **Pasternak JJ, McGregor DG, Lanier WL**. Effect of single-dose dexamethasone on blood glucose concentration in patients undergoing craniotomy. J Neurosurg Anesthesiol 2004; 16:122–125.
20. **Davidson J, Wilkinson A, Dantal J, et al; International Expert Panel**. New-onset diabetes after transplantation: 2003 international consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. Transplantation 2003; 75(suppl 10):SS3–SS24.
21. **American Diabetes Association**. Standards of medical care in diabetes—2011. Diabetes Care 2011; 34(suppl 1):S11–S61.
22. **Rodbard HW, Jellinger PS, Davidson JA, et al**. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract 2009; 15:540–559.
23. **Nathan DM, Buse JB, Davidson MB, et al; American Diabetes Association; European Association for Study of Diabetes**. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; 32:193–203.
24. **Axelrod L**. Corticosteroid therapy. In: Becker KL, editor. Principles and Practice of Endocrinology and Metabolism. 3rd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2000:752–763.
25. **Ferri FF, editor**. Practical Guide to the Care of the Medical Patient. 8th ed. Philadelphia, PA: Mosby/Elsevier; 2011.
26. **Kerrigan JR, Veldhuis JD, Leyo SA, Iranmanesh A, Rogol AD**. Estimation of daily cortisol production and clearance rates in normal pubertal males by deconvolution analysis. J Clin Endocrinol Metab 1993; 76:1505–1510.
27. **Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F**. Cortisol production rate in childhood and adolescence. J Pediatr 1990; 117:892–896.
28. **Esteban NV, Loughlin T, Yergey AL, et al**. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab 1991; 72:39–45.
29. **Lansang MC, Quinn SL**. Adrenal suppression. BMJ BestPractice 2010. http://bestpractice.bmj.com/best-practice/monograph/863/diagnosis/step-by-step.html. Accessed August 19, 2011.
30. **Zöllner EW**. Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled corticosteroids (part 2)—the risk as determined by gold standard adrenal function tests: a systematic review. Pediatr Allergy Immunol 2007; 18:469–474.
31. **Schuetz P, Christ-Crain M, Schild U, et al**. Effect of a 14-day course of systemic corticosteroids on the hypothalamic-pituitary-adrenal-axis in patients with acute exacerbation of chronic obstructive pulmonary disease. BMC Pulm Med 2008; 8:1.
32. **Kay J, Findling JW, Raff H**. Epidural triamcinolone suppresses the pituitary-adrenal axis in human subjects. Anesth Analg 1994; 79:501–505.
33. **Lansang MC, Farmer T, Kennedy L**. Diagnosing the unrecognized systemic absorption of intra-articular and epidural steroid injections. Endocr Pract 2009; 15:225–228.
34. **Duclos M, Guinot M, Colsy M, et al**. High risk of adrenal insufficiency after a single articular steroid injection in athletes. Med Sci Sports Exerc 2007; 39:1036–1043.
35. **Bong JL, Connell JM, Lever R**. Intranasal betamethasone induced acne and adrenal suppression. Br J Dermatol 2000; 142:579–580.
36. **Atabek ME, Pirgon O, Unal E**. Pituitary-adrenal axis suppression due to topical steroid administration in an infant. Pediatr Int 2007; 49:242–244.
37. **Ozerdem U, Levi L, Cheng L, Song MK, Scher C, Freeman WR**. Systemic toxicity of topical and periocular corticosteroid therapy in an 11-year-old male with posterior uveitis. Am J Ophthalmol 2000; 130:240–241.
38. **Chiang MY, Sarkar M, Koppens JM, Milles J, Shah P**. Exogenous Cushing's syndrome and topical ocular steroids. Eye (Lond) 2006; 20:725–727.
39. **Diprolene prescribing information**. Schering Corp 2005. www.theodora.com/drugs/diprolene_gel_005_schering.html. Accessed September 27, 2011.
40. **Villabona CV, Koh C, Panergo J, Reddy A, Fogelfeld L**. Adrenocorticotropic hormone stimulation test during high-dose glucocorticoid therapy. Endocr Pract 2009; 15:122–127.
41. **Ortega E, Rodriguez C, Strand LJ, Segre E**. Effects of cloprednol and other corticosteroids on hypothalamic-pituitary-adrenal axis function. J Int Med Res 1976; 4:326–337.
42. **Axelrod L**. Glucocorticoid therapy. Medicine (Baltimore) 1976; 55:39–65.
43. **Schürmeyer TH, Tsokos GC, Avgerinos PC, et al**. Pituitary-adrenal responsiveness to corticotropin-releasing hormone in patients receiving chronic, alternate day glucocorticoid therapy. J Clin Endocrinol Metab 1985; 61:22–27.
44. **Stewart PM**. The adrenal cortex. In: Kronenberg HM, editor. Williams Textbook of Endocrinology. 11th ed. Philadelphia, PA: Saunders/Elsevier; 2008.
45. **Hopkins RL, Leinung MC**. Exogenous Cushing's syndrome and glucocorticoid withdrawal. Endocrinol Metab Clin North Am 2005; 34:371–384.
46. **Richter B, Neises G, Clar C**. Glucocorticoid withdrawal schemes in chronic medical disorders. A systematic review. Endocrinol Metab Clin North Am 2002; 31:751–778.

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