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Safely Withdrawing Glucocorticoid Therapy: A Case-Based Approach

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Abstract

Glucocorticoids (GCs) have potent anti-inflammatory and immunomodulating effects, making them effective for treating various diseases. They are among the most commonly prescribed medications worldwide. The prevalence of GC therapy in the general population is estimated to be ~0.9 to 3%, though it is challenging to determine precisely. The chronic GC therapy is associated with severe morbidity and increased mortality due to iatrogenic Cushing's syndrome and suppression of the hypothalamic–pituitary–adrenal axis, leading to tertiary adrenal insufficiency. Therefore, it is not recommended to abruptly stop chronic GC therapy, and a gradual tapering of GCs is generally considered the ideal approach for GCs withdrawal. However, withdrawing GCs in patients on chronic therapy can be challenging due to the difficulty in accurately assessing HPA function. In this article, we aim to provide a practical, case-based approach to GC withdrawal based on current literature and our extensive experience in this field.

Keywords

- glucocorticoids withdrawal
- tapering
- glucocorticoids
- adrenal insufficiency
- iatrogenic cushing's syndrome
- GCs withdrawal syndrome

Introduction

Since they became commercially available in the 1940s, glucocorticoids (GCs) have been among the most widely prescribed medications.[1] While the true prevalence of GC therapy in the general population is challenging to determine, it has been estimated to be between 0.9 and 3.0%.[2–5] GCs have potent anti-inflammatory and immunomodulating effects, making them a desirable therapy for a multitude of diseases,[6] but chronic GC therapy is also associated with severe morbidity and higher mortality as it can cause iatrogenic Cushing's syndrome and suppress the hypothalamic–pituitary–adrenal (HPA) axis, resulting in tertiary adrenal insufficiency (AI).[7–9] Abrupt cessation of chronic GC therapy is therefore not recommended, and a protracted weaning from GCs is typically regarded as an ideal therapeutic approach. However, withdrawal can be challenging because of the difficulty of adequately assessing underlying HPA function. In this article, we aim to provide a practical approach to GC withdrawal based on the current literature and our own extensive experience in this area using a case-based approach (►**Case 1**).

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Case 1 Study case

A 35-year-old woman was referred to the endocrinology team for assessment of her underlying adrenal status and the possibility of safe withdrawal of glucocorticoid (GC) therapy. GC therapy had been started 3 months previously for lupus nephritis; she was initially administered intravenous methylprednisolone pulse therapy followed by 40 mg of daily oral prednisone. As her disease went into remission, the rheumatology team began tapering her GC therapy. While she tolerated the initial taper over a period of 3 weeks without any problem, she began experiencing generalized fatigue and arthralgias when the prednisone dose was decreased to 10 mg daily. The primary referral queries were whether the patient had adrenal insufficiency and what the best approach might be to wean her off GC therapy

Glucocorticoid Formulations

GCs are available in various formulations, including oral, inhaled, injection, and topical, which are further subdivided based on the duration of their biologic activity into short-, intermediate-, and long-acting preparations (►**Table 1**).[10] Notably, GC-induced AI has been reported with all GC formulations,[11–13] and while there is some uncertainty about the amount and duration of exogenous GCs that are associated with HPA suppression,[9] it is generally assumed that any patient taking more than the equivalent of 5.7 mg/m^2/d of cortisol (►**Table 1** for equivalent doses) is at risk of AI,[14] although a short course (less than 3 weeks) of low-dose GC therapy confers a low risk.[15] For adults, assuming an average surface area of 1.7 m^2, this equates to ~10 mg of hydrocortisone (HC) per day.[16,17]

Glucocorticoid-induced AI

Symptoms of insidious AI are nonspecific and require a high index of suspicion; they can include fatigue, nausea, vomiting, and in some cases significant weight loss.[18] GC withdrawal syndrome (GWS) symptoms are similar to AI symptoms, but GWS may include other, more noticeable symptoms, such as fever, skin desquamation, arthralgia, and mood swings.[19] GWS can occur even with supraphysiologic doses of GCs if they are rapidly tapered after prolonged treatment, as evidenced by the case described earlier. In such a situation, a protracted taper of GCs can be useful in restoring the HPA axis by increasing adrenocorticotropic hormone (ACTH) levels and thus re-establishing normal adrenal function and endogenous cortisol secretion.[18] Full recovery from GC-induced AI can vary, with ~60% of patients recovering adrenal function over 1 to 2 years.[20]

Diagnosing GC-induced AI is further complicated by the interaction of certain synthetic GCs with commercial serum cortisol assays, which makes correct assessment of endogenous cortisol activity exceedingly challenging.[21] In addition, cortisol is ~90% bound to cortisol-binding globulin (CBG), and variations in CBG levels (such as in pregnancy, liver cirrhosis, inflammation, and critical illness) can further impact the interpretation of cortisol levels and the diagnosis of AI.[22] Therefore, a thorough assessment of these factors should be undertaken prior to initiating GC withdrawal.

While there are other testing modalities available for AI diagnosis, they are not widely used. Salivary cortisol tests are relatively new and are a promising measure of free cortisol that is unaffected by CBG status.[23] However, their utility is currently limited by a lack of validated reference values and by significant kit-to-kit variability.[24] Serum dehydroepiandrosterone sulfate (DHEAS), when normal (based on age- and sex-specific reference range), makes AI unlikely. The combination of serum DHEAS levels with serum cortisol levels can provide valuable insights into evaluating adrenal function.[25]

Table 1 The equivalent dose, glucocorticoid potency, and impact on HPA suppression of various glucocorticoid preparations

	Equivalent dose (mg)	Glucocorticoid potency	HPA suppression	Duration of action (h)
Short acting				
Hydrocortisone (cortisol)	20	1.0	1.0	8–12
Cortisone acetate	25	0.8		8–12
Intermediate acting				
Prednisone	5	4	4	12–36
Prednisolone	5	4		12–36
Methylprednisolone	4	5	4	12–36
Triamcinolone	4	5	4	12–36
Long acting				
Dexamethasone	0.75	30	17	36–72
Betamethasone	0.6	30		36–72

Abbreviation: HPA, hypothalamic–pituitary–adrenal.
Source: Adapted from Nicolaides et al. (2000).[17]

Withdrawal Protocol

GC withdrawal is considered in several situations, such as reaching a maximum desired therapeutic outcome, lack of therapeutic benefit after a sufficient trial period, or uncontrolled side effects of GC therapy. In patients who have received GC treatment for less than 3 weeks and at a dose of less than 10 mg prednisolone daily (or equivalent), GCs can be stopped without tapering. However, it is important to note that GC-induced AI can still occur even with short-term use, especially in patients who have previously taken GCs intermittently. Therefore, if the patient experiences symptoms of AI after discontinuing GCs, it is recommended that morning serum cortisol levels be tested. For those patients who have received high-dose GCs (10 mg or more prednisolone or equivalent) for longer than 3 weeks, we suggest the following protocol (►**Fig. 1**).

Step 1: Taper Glucocorticoids Therapy

Once it has been established that the patient no longer requires GC therapy, the dose should be gradually reduced to a range of 5.0 to 7.5 mg of daily prednisolone (or its equivalent). Close monitoring of the patient should be undertaken to avoid any symptoms of GWS. If the patient has Cushing's syndrome or experiences intolerable GWS symptoms during tapering, it is recommended to return to the previous dose and then proceed with a slower tapering regimen using even smaller dose reductions over a longer duration. The proposed dose-tapering scheme is shown in ►**Table 2**.

Rationale

Clinicians should always consider withdrawing GCs as soon as clinically feasible. While there is no universally accepted optimal tapering scheme, there is broad consensus that tapering should be done gradually until a "physiological" dose is reached. Most randomized clinical trials on tapering have been conducted for specific conditions, such as rheumatoid arthritis or multiple sclerosis. Initially, such trials are guided by the management of the underlying disease and only later focus on gradually weaning off GCs.[26,27] It is therefore advisable to consider GC withdrawal only after the stabilization of the primary disease. A safe tapering protocol requires a clear communication between the physician and patient, with a focused discussion about GWS and how to manage such symptoms. We tend to provide both verbal and written directions to our patients to educate them regarding GWS, and we advise them to step up the dose if

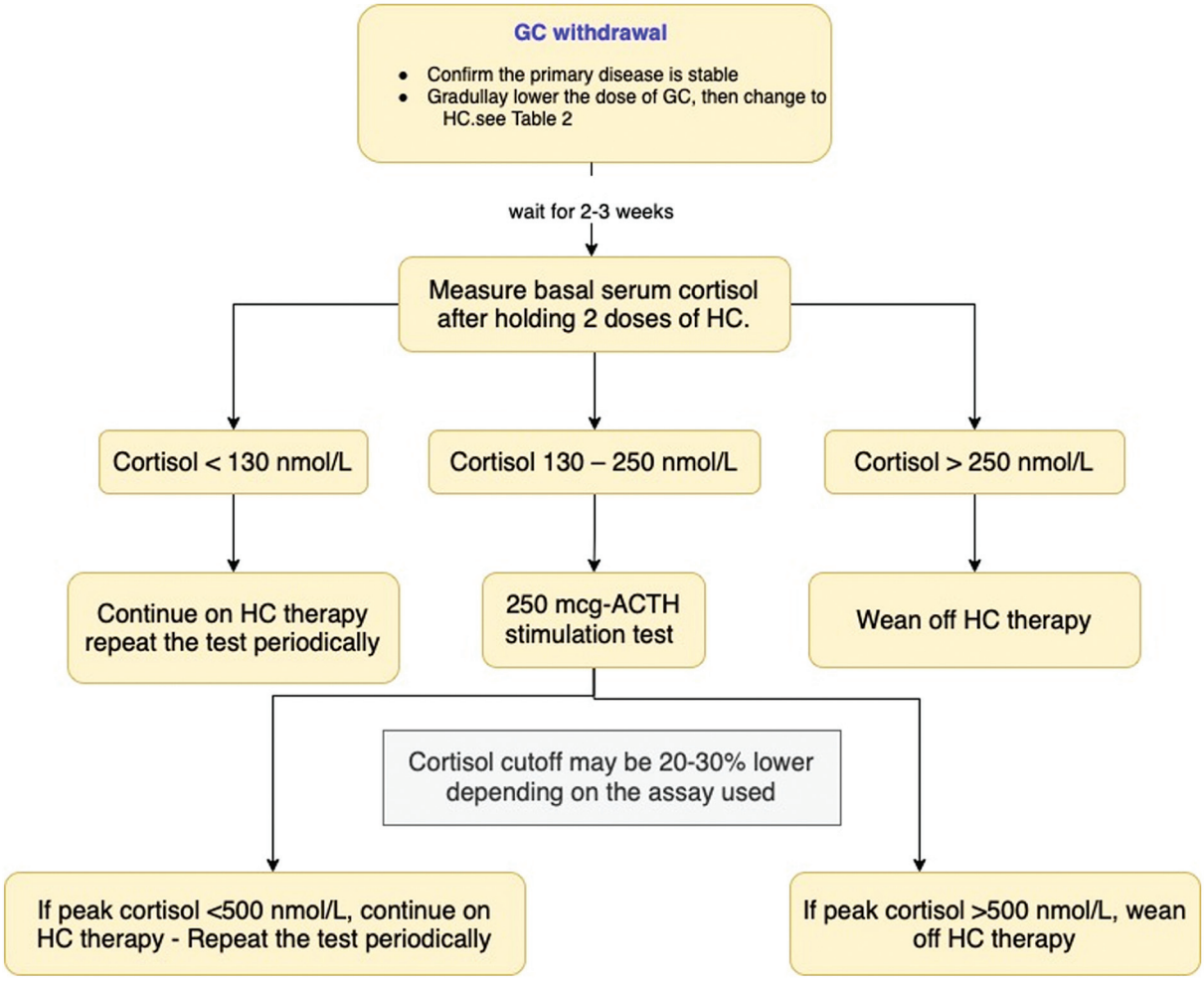

Fig. 1 Practical protocol for GC withdrawal. ACTH, adrenocorticotropic hormone; GC, glucocorticoid; HC, hydrocortisone.

Table 2 The dose-dependent effects of glucocorticoids

Dose[a]	No cushingoid features	GWS or cushingoid features
More than 40 mg/d	5–10 mg every 1–2 wk	2.5–5.0 mg every 2–3 wk
20–40 mg/d	5 mg every 1–2 wk	2.5 mg every 2–3 wk
7.5–20 mg/d	2.5 mg every 1–2 wk	1 mg every 1–2 wk
7.5 mg/d or less	Change to HC, 10 mg morning, 5 mg midday, and 5 mg evening	

Abbreviation: GWS, glucocorticoid withdrawal syndrome.
[a]Prednisone or equivalent. For nonoral GC, start hydrocortisone replacement once ready to discontinue GC therapy.

symptoms become intolerable. In patients at risk for GWS, smaller dose reductions should be implemented over an extended duration to minimize potential adverse effects.[28]

Step 2: Start Hydrocortisone Therapy

Once patients have successfully tapered to an oral GC dose equivalent to HC 20 mg daily (►**Table 1**), we switch them to oral HC 10 mg morning, 5 mg midday, and 5 mg evening and then, after 1 to 2 weeks, decrease the dose to 10 mg morning and 5 mg evening. In patients taking nonoral GCs, for which dose equivalence is difficult to calculate, we start oral HC as above and rapidly taper the nonoral GC while keeping them on HC therapy.

Rationale

HC has a relatively short half-life, and the use of long-acting GCs can affect morning cortisol test results.[29] HC is also chemically identical to endogenous cortisol, which can potentially interfere with commercial cortisol assays if the tests are not conducted properly.[30]

Step 3: Draw Basal Serum Cortisol Levels

Once the patient has been established on oral HC therapy, as described earlier, it is advisable to wait for 2 to 3 weeks (or longer in the case of chronic GC therapy of more than 3 months). This allows sufficient time to ensure that the patient is on a stable HC regimen. Basal serum cortisol levels should be obtained as follows:

- Instruct the patient to omit the evening 5 mg dose of HC.
- The next morning, before the patient takes their morning dose of HC, obtain a sample of serum cortisol within 1 to 2 hours of waking (typically 7 a.m.–9 a.m.).
- Advise the patient to continue their regular HC regimen, as prescribed, after the test.
- If the patient is distressed or symptomatic, it may be necessary to postpone the test and perform it at a more suitable time.

Rationale

It is recommended to wait for 2 to 3 weeks to allow recovery for HPA axis and to ensure stability of the underlying disease. As the dose of GC therapy is reduced, the HPA axis may gradually recover, leading to an increased production of ACTH. Such a rise in plasma ACTH levels promotes the recovery of adrenal function, ultimately resulting in the restoration of endogenous cortisol production.[31,32] Basal serum cortisol is best measured between 7 a.m. and 9 a.m. in patients with suspected AI.[33]

Step 4: Assess Basal Cortisol Activity

A serum cortisol draw, as per Step 3, should give a true endogenous basal cortisol value.

- Basal serum cortisol of less than 130 nmol/L indicates insufficient endogenous cortisol activity. The patient should continue with GC therapy. It is recommended that basal serum cortisol be checked periodically, as per Step 3, on an ongoing basis.
- Basal serum cortisol of 250 nmol/L or more indicates adequate endogenous cortisol activity, and the patient may discontinue GC therapy.
- If basal serum cortisol is between 130 and 250 nmol/L, an ACTH stimulation test may be required to ascertain the underlying adrenal status. A post-ACTH cortisol of 500 nmol/L or more indicates adequate cortisol activity, and GC therapy can then be safely discontinued. Note that, for newer cortisol assays, the cutoff may be as low as 386 nmol/L.[34]

Step 5: Confirmation of HPA Recovery

Once it has been confirmed that the patient has adequate endogenous cortisol activity based on basal serum cortisol and/or an ACTH stimulation test, GC therapy can be tapered to a stop over the next few days. This can be followed by a final ACTH stimulation test after 4 to 6 weeks to confirm full recovery, based on clinical judgment, to confirm that the patient has regained HPA axis function (►**Table 2**)

Rationale

Basal serum cortisol provides a robust preliminary assessment of underlying endogenous cortisol activity.[35,36] A very low basal cortisol of less than 130 nmol/L reliably excludes adrenal recovery, and such patients should continue GC therapy. On the other hand, a basal serum cortisol of more than 250 nmol/L indicates recovery of the HPA axis, and such patients can be safely weaned off GC therapy. Patients with basal cortisol between these two levels require an ACTH stimulation test,[36] also known as a short synacthen test, which typically requires serum cortisol to be measured at 0, 30, and 60 minutes following either intravenous or subcutaneous administration of 250 µg of synthetic ACTH. The interpretation of the ACTH stimulation test is based on the 30- or 60-minute serum cortisol; we recommend using the

60-minute cortisol level to avoid false-negative results.[37] An adequate response to an ACTH stimulation test is typically defined as more than 500 nmol/L, but depending on the assay, some studies have suggested a cutoff of more than 386 nmol/L.[34,38,39] Notably, many patients who may initially fail to show signs of HPA recovery still recover after several years,[40] so ongoing testing is crucial to avoid unnecessary GC therapy. The use of a final ACTH stimulation test 4 to 6 weeks after discontinuing GC therapy may be considered, based on clinical judgment, to confirm that the patient has regained HPA axis function.

Conclusion

The case described herein (**Box 1**) illustrates a frequently encountered clinical scenario. Our patient was on a daily dose of prednisone 10 mg for several weeks and had been unable to tolerate further tapering of GC therapy. To avoid GWS, we began a very gradual taper by dropping the dose by no more than 1 mg every 2 weeks. Once she achieved a dose of 5 mg, we transitioned her to HC, 10 mg morning and 5 mg evening. After 3 weeks on this regimen, we conducted a basal serum cortisol test, as per the above protocol, which revealed a cortisol level of 273 nmol/L. Based on this result, HC was discontinued, and an ACTH stimulation test was performed 6 weeks later, which showed a 60-minute cortisol level of 590 nmol/L, indicating a complete recovery of the HPA axis (►**Fig. 1**).

Authors' Contribution
All the authors contributed equally to this study.

Conflict of Interest
None declared.

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