Glucocorticoid Tapering: Pitfalls to Avoid and Shared

Abstract:

Adrenal insufficiency is a fairly common and undesirable complication in patients undergoing long-term corticosteroid therapy. This necessitates specific prescribing guidelines as well as measures for evaluating, diagnosing, and managing complications related to damage to the hypothalamic-pituitary-adrenal (HPA) axis.

Therefore, in this paper, we have attempted to highlight the clinical symptoms, laboratory tests, and best practice recommendations necessary for both the appropriate prescribing and optimal management of corticosteroid therapy and such a delicate yet critical complication as adrenal insufficiency.

Introduction

"When in doubt, add corticosteroids!" is perhaps the most quoted adage across multiple medical disciplines. Synthetic glucocorticoids (GC) are widely used for their anti-inflammatory, immunosuppressive, and anti-allergic properties [1].

Long-term corticosteroid therapy affects approximately 1% of the general population. The most feared adverse effect is suppression of the hypothalamic-pituitary-adrenal (HPA) axis, leading to adrenal insufficiency upon discontinuation. Risk factors for glucocorticoid-induced adrenal insufficiency (GC-IAI) include duration of glucocorticoid therapy, dose and potency of the agent, route of administration, and individual susceptibility. A cautious tapering approach combined with appropriate patient counseling is essential to ensure successful withdrawal [1, 2].

Physiological Background

Glucocorticoids that enter the systemic circulation directly—as well as those that survive first-pass metabolism following gastrointestinal absorption—exert negative feedback on corticotropin-releasing hormone (CRH)-producing neurons and on the corticotroph cells of the anterior pituitary. This results in reduced adrenal cortisol production and, following prolonged exposure, hypoplasia and atrophy of the adrenal cortex.

Upon discontinuation of corticosteroid therapy, the negative feedback on the HPA axis is lifted, leading first to recovery of CRH and ACTH secretion, followed by restoration of cortisol production. However, cortisol production may remain suppressed long-term if adrenal atrophy has occurred [2, 3].

Diagnosis of Post-Corticosteroid Adrenal Insufficiency

Clinical Features

The clinical presentation resembles primary adrenal insufficiency, but WITHOUT hyperpigmentation (melanodermia) or mineralocorticoid deficiency. The symptomatologyistypicallylesssevere and mayinclude:

- Tendency toward hypotension (loss of cortisol-mediated vascular tone)
- Anorexia and nausea
- Fatigue, general malaise, and near-syncope (presyncope)
- Arthralgia and myalgia
- Depressivesymptoms

LaboratoryFindings

Salt wasting does not occur in corticotroph insufficiency because aldosterone secretion remains intact. Hyponatremia, when present, is secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) driven by cortisol deficiency. Hypotension, if present, results from loss of cortisol's permissive effect on vascular tone. Hypoglycemia is possible but uncommon. Hyperkalemia is not observed given preserved mineralocorticoid function.

Clinical Pitfalls

These signs are often difficult to identify in patients with chronic underlying disease, as disease flares following treatment discontinuation may produce overlapping or intertwined symptoms. Furthermore, fatigue accompanying GC discontinuation may reflect loss of the psychostimulant effect of glucocorticoids, independent of corticotroph insufficiency [3].

> *"Signs of corticotroph insufficiency may go unnoticed or be misinterpreted."*

It is therefore imperative that healthcare professionals maintain a high index of suspicion for adrenal insufficiency during glucocorticoid tapering.

Current Guidelines

The joint clinical practice guideline from the European Society of Endocrinology (ESE) and the Endocrine Society, published in May 2024 [1], provides guidance on glucocorticoid tapering to prevent adrenal insufficiency.

These recommendations are not intended to replace clinical judgment and may require adaptation to local circumstances.

The second group of recommendations is detailed below, as these are considered the most clinically important.

1. General Recommendations for Corticosteroid Use in Non-Endocrine Conditions and Patient Education

- Patients on corticosteroids or undergoing dose tapering for non-endocrine conditions do not require specialist endocrinology evaluation.
- Patients receiving corticosteroids should have access to current and appropriate information regarding the various endocrine aspects of corticosteroid therapy.

2. Recommendations on Tapering of Systemic Glucocorticoids for Non-Endocrine Conditions, Diagnosis and Management of GC-Induced Adrenal Insufficiency, and Glucocorticoid Withdrawal Syndrome

- We suggest NOT tapering glucocorticoids in patients on short-term treatment (<3–4 weeks), regardless of dose. In such cases, GCs may be discontinued without testing due to the low risk of HPA axis suppression. Oral GC exposure carrying a risk of adrenal insufficiency must exceed the following two thresholds:
  - Duration: 3–4 weeks or more
  - Any supratherapeutic dose: above the daily equivalent of 15–25 mg of hydrocortisone
- Dose reduction in patients on long-term treatment should only be attempted when the underlying disease for which GCs were prescribed is controlled and GCs are no longer required. In such cases, GCs are tapered until the physiological daily dose equivalent is reached (e.g., prednisone 4–6 mg/day).

Glucocorticoid Withdrawal Syndrome: Symptoms experienced during dose reduction within the supratherapeutic range that are not attributable to the underlying disease and—by definition—not due to untreated adrenal insufficiency. If patients develop GC withdrawal syndrome symptoms during tapering, clinicians may consider slightly increasing the GC dose and attempting a slower taper [4].

- Experts do not recommend routinely testing for adrenal insufficiency in patients receiving supratherapeutic GC doses or those who still require GCs for their underlying disease. Conversely, intermediate- or short-acting GCs, which have both a shorter biological half-life and lower GC potency, are more likely to allow HPA axis recovery.
- It is suggested that patients receiving a daily GC dose equivalent to the physiological dose who wish to discontinue GC therapy should either:
  - Continue to gradually taper the GC dose under clinical monitoring for signs and symptoms of adrenal insufficiency, or
  - Undergo testing with a morning serum cortisol measurement
- If confirmation of HPA axis recovery is required, morning serum cortisol measurement is recommended as the first-line test. The serum cortisol value should be interpreted as a continuum, with higher values being more indicative of HPA axis recovery. Of note, salivary cortisol is gaining increasing interest as a less invasive alternative for evaluating patients with suspected adrenal insufficiency.
- Routine dynamic testing to diagnose adrenal insufficiency is not recommended in patients tapering or discontinuing glucocorticoid therapy. As stated in Recommendation 7, morning serum cortisol is the first-line test when long-term corticosteroid discontinuation is being considered. The short Synacthen (cosyntropin) stimulation test remains the gold-standard dynamic test; however, it should be noted that it only assesses the direct adrenal gland response to supratherapeutic ACTH stimulation.
- We suggest raising patient awareness of the possibility of GC-induced adrenal insufficiency in the following scenarios:
  - Current or recent use of non-oral GC formulations with signs and symptoms of adrenal insufficiency

    - Concurrent use of multiple GC formulations
    - Use of high-dose inhaled or topical glucocorticoids
    - Use of inhaled or topical glucocorticoids for more than one year
    - Receipt of intra-articular glucocorticoid injections within the preceding 2 months
    - Concomitant treatment with potent cytochrome P450 3A4 inhibitors
- Patients on current or prior GC therapy presenting with signs and symptoms of exogenous Cushing's syndrome should be considered to be at risk of GC-induced adrenal insufficiency.
- Fludrocortisone is NOT recommended in patients with GC-induced adrenal insufficiency, as mineralocorticoid function is preserved.

3. Recommendations on Diagnosis and Management of Adrenal Crisis in Patients with GC-Induced Adrenal Insufficiency

- Patients who are currently taking or have previously taken corticosteroids without a cortisol level to exclude adrenal insufficiency should receive stress-dose corticosteroid coverage when exposed to physiological stressors.
- Oral corticosteroids should be used for minor stress in the absence of hemodynamic instability or protracted vomiting or diarrhea.
- Parenteral corticosteroids should be used for moderate-to-major stress, procedures under general or regional anesthesia, procedures precluding oral intake, or in the presence of hemodynamic instability or protracted vomiting or diarrhea.
- In patients who are taking or have previously taken corticosteroids without a cortisol level, and who present with hemodynamic instability, vomiting, or diarrhea, the diagnosis of adrenal crisis should be considered regardless of GC type, route of administration, or dose. Patients with suspected adrenal crisis should be treated promptly with parenteral corticosteroids and correction of fluid and electrolyte disturbances [5].

Patient Education

- The phrase "in case of stress" should be avoided when indicating when to increase the hydrocortisone dose or initiate treatment.
- The instruction should instead specify "physical stress" — not psychological stress, except in very particular circumstances.
- Similarly, the frequently used instruction "double the dose" is misleading.
- The correct approach is to immediately take the usual hydrocortisone (HC) dose orally and then distribute the additional amount (that would have been doubled) across 3 time points throughout the day, mimicking the physiological adrenal stress response [6].

Conclusion

- The evidence supporting most of the above recommendations regarding GC-induced adrenal insufficiency is of low to very low quality.
- Salivary cortisol measurement will likely play an increasing role in future practice.
- In the meantime, serum cortisol should be interpreted as a continuum, given that cortisol effects vary between patients and that current thresholds remain relatively arbitrary.
- Patient education and awareness remain a cornerstone of successful glucocorticoid tapering.

- Accordingly, significant work remains to better predict the occurrence of adrenal insufficiency during GC withdrawal.

References

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