How to manage withdrawal of glucocorticoid therapy

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Our series on stopping drugs provides practical advice on why, when and how to withdraw drug therapy. Here the authors discuss the issues arising from discontinuing glucocorticoid therapy.

Glucocorticoids are the most powerful of all anti-inflammatory agents and are used successfully to treat a wide variety of diseases. Long-term glucocorticoid therapy is, however, associated with a number of adverse sequelae including diabetes, hypertension, loss of bone mass and somatic changes characteristic of Cushing’s syndrome.

Often overlooked, however, is the concurrent suppression of the endogenous hypothalamic-pituitary-adrenal (HPA) axis, which may persist long after exogenous steroid therapy is discontinued. Importantly, this suppression renders the endogenous system unable to respond appropriately to stresses relating to illness, trauma, and even emotion, leaving the individual at risk of developing life-threatening adrenal insufficiency crisis.

The dogma that adrenal crises secondary to withdrawal of glucocorticoid therapy are infrequent has recently been questioned, however, with a suggestion that inappropriate discontinuation or excessively rapid dose reduction may be the most frequent cause of adrenal insufficiency crises.1,2 Transient nonspecific symptoms following steroid withdrawal are common, and significantly more so than true adrenal crises.

In this article we will discuss who is at risk, and how to manage withdrawal of glucocorticoid therapy. We will, however, not discuss issues around resurgence of the primary disease with reduction in steroid dosage as this should be tailored to the individual disease state.

**Physiology of the HPA axis**

The adrenal gland consists of two separate functional entities, the cortex and the...
The cortex accounts for 90 per cent of the gland and is responsible for production and secretion of mineralocorticoids, glucocorticoids and adrenal androgens. The predominant glucocorticoid is cortisol, secretion of which is controlled by pituitary adrenocorticotropin hormone (ACTH), which in turn is controlled by the hypothalamic hormone, corticotropin-releasing hormone (CRH; see Figure 1). Secretion of CRH and ACTH is regulated by feedback of cortisol at the level of the hypothalamus and pituitary respectively.

Endogenous cortisol production equates to approximately 5–7 mg per m² per day,1,4 which after allowing for bioavailability is equivalent to approximately 15–20 mg oral hydrocortisone per day.5 During physical and psychological stress levels of ACTH and cortisol increase significantly, mediated by both CRH and vasopressin.

Cortisol secretion shows a pronounced diurnal rhythm.6 Blood levels increase from 02.00–03.00 hours, peak at 06.00–07.00 hours, falling thereafter through the day to reach a nadir at around 24.00 hours.6 Imposed upon the normal diurnal rhythm, cortisol levels increase rapidly in response to physical and emotional stresses. The majority of circulating cortisol is bound to cortisol-binding globulin (75–80 per cent) and albumin (10–15 per cent), leaving only 5–6 per cent free to pass through cell membranes and initiate physiological responses.

In the cell cortisol binds the cytosolic glucocorticoid receptor (GCR), following which this complex enters the nucleus and binds DNA to regulate transcription.

Most steroids used in clinical practice are synthetic analogues of cortisol (hydrocortisone), brought about by modification of the basic molecular structure to emphasise particular pharmacokinetic or pharmacodynamic attributes. Cortisone, the naturally occurring metabolite of cortisol, when given systemically is converted in the liver to cortisol. Synthetic glucocorticoid analogues (ie prednisolone, budesonide, dexamethasone) are generally used in clinical practice due to their longer half-lives, lower mineralocorticoid action and greater anti-inflammatory potency. Dexamethasone is the only glucocorticoid

<table>
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<tr>
<th>Symptoms</th>
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<tbody>
<tr>
<td>gastrointestinal</td>
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<tr>
<td>nausea, vomiting, anorexia, weight loss, abdominal pain, diarrhoea general malaise and weakness</td>
</tr>
<tr>
<td>lethargy</td>
</tr>
<tr>
<td>postural dizziness</td>
</tr>
<tr>
<td>arthralgia, myalgia</td>
</tr>
<tr>
<td>mood swings, emotional lability</td>
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| Signs |
| postural hypotension |
| alabaster pale skin (ACTH suppressed) |
| fever |

| Biochemistry |
| hyponatraemia |
| hypoglycaemia |
| lymphocytosis, eosinophilia |
| hypercalcaemia (rare) |

Table 1. Symptoms, signs and blood profile of patients with adrenal suppression resulting from glucocorticoid therapy analogue devoid of mineralocorticoid action.

Who is at greatest risk of HPA axis suppression?
The ability of glucocorticoid analogues to suppress the HPA axis correlates with both potency (ie anti-inflammatory effect) and duration of biological effect.7 Dexamethasone is the most potent glucocorticoid analogue (25-fold that of cortisol) used in clinical practice, and with a prolonged biological effect of 36–54 hours produces the greatest suppression of the HPA axis. Prednisolone, triamcinolone and methylprednisolone are moderately suppressive, whereas hydrocortisone and deflazacort (Calcort) are short acting and the least potent and thus the least suppressive.

HPA axis suppression is less likely if the endogenous axis is allowed to recover between doses. The use of pulse therapy, alternate-day therapy or glucocorticoids with short half-lives reduces the risk of suppression. Systemic glucocorticoids result in significantly greater risk of suppression than intra-articular, inhaled, nasal or topical glucocorticoids.

Use of glucocorticoids in the evening inflicts greater attenuation of the early morning ACTH surge; therefore, where possible glucocorticoids should be administered as a single dose in the morning.

Hydrocortisone and cortisol acetate are short acting and must be given at least twice daily. Concomitant medications influence the risk glucocorticoid-induced HPA suppression, most commonly by either increasing, ie phenytoin, rifampicin, or decreasing, ie oestrogens, ketoconazole, metabolism of the exogenous glucocorticoid.

Dose and duration of glucocorticoid therapy along with other variables act only as a guide to individuals who are at the greatest risk of HPA axis suppression rather than being predictive.8,10 Clinically relevant adrenal insufficiency is rare in patients treated for less than one to two weeks, and if this does occur is likely to be short lived.11,12 Patients treated with supraphysiological glucocorticoid doses for more than two weeks, particularly where a dose of prednisolone 20 mg once daily or equivalent is used, should be assumed to be at risk of HPA axis suppression.

Considerations when Withdrawing Glucocorticoids
When reducing long-term glucocorticoid therapy to a dose equivalent to physiological, or lower, a number of individuals exhibit nonspecific symptoms. In this setting there are three scenarios to be considered,13,14 all of which respond clinically to increasing the glucocorticoid dose:

• steroid withdrawal syndrome
• adrenal insufficiency
• recurrence of the disease being treated.

Steroid withdrawal syndrome
Steroid withdrawal syndrome is defined by symptoms of glucocorticoid deficiency in the setting of a proven normal HPA axis.16 Dependence can be physical, psychological or a combination of both. Individuals complain of a variable combination of general malaise, lethargy, postural dizziness, generalised weakness, arthralgia, headaches, mood swings and emotional lability.

The syndrome can be observed with reductions in glucocorticoid dosage even when the current dosage remains
Figure 2. Suggested pathway for withdrawal of prednisolone or hydrocortisone therapy having reduced to ‘physiological’ levels. The pathway is only a guide and withdrawal regimens should be individualised to each patient. After withdrawal of glucocorticoids in patients that remain asymptomatic, and in the absence of formal testing of the endogenous axis, they should be considered at risk of adrenal insufficiency for the 12 months following withdrawal.
supraphysiological. When steroid doses are below physiological, it is imperative to rule out adrenal insufficiency. Despite the sometimes florid symptoms, patients are not at risk of adrenal insufficiency crises.

The underlying mechanism of the steroid withdrawal syndrome is poorly understood but is postulated to relate to glucocorticoid-induced changes in several mediators including CRH, vasopressin, pro-opiomelanocortin, cytokines and the adrenergic system. 17

The syndrome is self-limiting and treatment is by reinstatement of the lowest dose of glucocorticoids that negate the symptoms. Thereafter, very slow withdrawal of the exogenous glucocorticoid over a period of several months should be undertaken.

Adrenal insufficiency

Most important in symptomatic patients on a dose of glucocorticoid reduced to physiological, or below, and where the primary disease has not relapsed is to rule out adrenal insufficiency. 2,18 Symptoms of adrenal insufficiency are indistinguishable from steroid withdrawal syndrome, and include lethargy, anorexia, nausea, vomiting, abdominal pain, weakness, weight loss, postural dizziness, myalgia and arthralgia (see Table 1).

Notably many patients with adrenal insufficiency remain well until concurrent illness or stress occurs when they may decompensate. Presenting with acute severe symptoms, marked postural hypotension, dehydration, shock and coma. Biochemical abnormalities of hypoglycaemia and hypoglycaemia are most common when individuals decompensate. This is a life-threatening situation that requires emergency treatment with intravenous normal saline, correction of hypoglycaemia and high-dose intravenous hydrocortisone.

Suppression of the HPA axis is primarily central in nature, though with longer duration of glucocorticoid therapy secondary adrenal atrophy may occur. 6,13 Central suppression results from feedback of the exogenous glucocorticoid at the hypothalamus and pituitary gland to inhibit release of CRH and ACTH respectively. After an acute insult to the hypothalamic–pituitary axis that leads to ACTH deficiency, atrophy of the adrenal glands occurs within six weeks.

Tests of HPA axis integrity

The diagnosis of adrenal insufficiency resulting from glucocorticoid therapy needs to be confirmed biochemically as symptoms and signs are nonspecific. Furthermore, only the biochemistry differentiates adrenal insufficiency from the steroid withdrawal syndrome.

When testing the HPA axis it is important that exogenous steroids, with the exception of dexamethasone, are withdrawn due to variable cross-reactivity in the cortisol assay. For patients on hydrocortisone reliable testing can be performed the morning after the previous evening dose, and for those on daily prednisolone tests can be performed 24 hours after the previous dose.

Measurement of urinary free cortisol or plasma ACTH has no role in assessing integrity of the endogenous HPA axis. 14 The simplest test is the 9am cortisol level. 19 A value <100 nmol per litre is suggestive of cortisol insufficiency, and >450 nmol per litre is consistent with cortisol sufficiency. 20

The majority of individuals with both a normal and impaired cortisol axis will, however, have values of between 100 and 449 nmol per litre. Further 9am cortisol levels can be obtained in the hope of achieving a value >450 nmol per litre, though it is probably more appropriate to go on to perform a stimulation test.

There are a number of stimulation tests to assess the HPA axis. These can be divided into tests that directly stimulate the adrenal gland – short synacthen test (SST) – and those that test the hypothalamus, pituitary and adrenal gland – glucagon stimulation test (GST), insulin tolerance test (ITT), metyrapone test and CRH test. Both the metyrapone and CRH tests are plagued by false negative results and are therefore now infrequently used.

The SST is simple and has excellent sensitivity and specificity for detection of adrenal insufficiency. The test involves measurement of baseline cortisol, followed by synacthen 250 µg im or iv, with further measures of cortisol at 30 and 60 minutes postinjection. 21 Intramuscular injection avoids the small risk of anaphylaxis associated with iv injection. A normal response is a peak cortisol value >550 nmol per litre. This cut-off value varies depending on the cortisol assay used and it is important to liaise with the local endocrine laboratory.

The SST entails direct stimulation of the adrenal gland and does not formally test the hypothalamus and pituitary, and therefore can result in false negative results where secondary adrenal atrophy has not occurred. 21,22

Both GST and ITT examine the integrity of the complete HPA axis. Both are more invasive than the SST and should therefore be performed only in secondary care by experienced staff.

A guide to withdrawing glucocorticoid therapy

It is important to note that not all individuals treated with long-term glucocorticoid therapy develop HPA axis suppression. Additionally, there are no prospective studies on the best way to withdraw glucocorticoid therapy, 13 and therefore most clinicians who regularly use glucocorticoids have developed their own withdrawal regimens that work well for them. 10,23 It is safest, however, to assume that any individual who has received supraphysiological glucocorticoid therapy for more than two weeks is at risk of HPA axis suppression.

The rate of reduction in glucocorticoid dosage to physiological equivalents, and whether glucocorticoids should be fully withdrawn, is generally dependent on activity of the disease being treated. Significant glucocorticoid-aggravated morbidity such as herpetic keratitis, difficult-to-control diabetes mellitus, severe hypertension, worsening osteoporosis and steroid-induced psychosis will also expedite the decision to rapidly reduce or completely withdraw glucocorticoids.

On approaching physiological levels of glucocorticoids many physicians continue to taper the dose, but at a reduced rate, without testing the adequacy of the endogenous system as long as the patient remains asymptomatic. An example of this would be on lowering of prednisolone dose to 5mg once daily – the dose could then be reduced by 1mg every two to four weeks. Before fully discontinuing gluco-
Glucocorticoids alternate-day therapy may aid recovery of the endogenous axis.

An alternative philosophy on reducing the steroid dose to physiological levels is to change to hydrocortisone due to its short duration of action, which may aid recovery of the endogenous HPA axis. Patients in whom steroids are withdrawn as above and who remain asymptomatic should be advised that, should they become unwell in the following 12 months, they may require glucocorticoid supplementation.

Where glucocorticoid doses have been reduced below physiological, resulting in symptoms, investigation of the HPA axis is required. If a 9am cortisol level is neither diagnostic of cortisol insufficiency or sufficiency, a stimulation test should be performed. When this confirms cortisol insufficiency, very slow reduction of glucocorticoid dosage can be continued until weaned.

Patients with random cortisol levels <100nmol per litre or significantly impaired responses to stimulation should be commenced on physiological glucocorticoid replacement (hydrocortisone 15–20mg per day or prednisolone 4–5mg per day). Advice regarding the need to increase their steroid dose two to three fold with moderate illness is essential, and it must be explained that they will require parenteral glucocorticoids with severe illness.13,24

Patients should be prescribed hydrocortisone for injection and taught how to use this in an emergency. A steroid card and appropriate medical emergency bracelet or pendant should be strongly recommended.13

After an intervening period of three to four months a further assessment of putative recovery of the endogenous cortisol axis can be performed. Where only a mildly abrogated cortisol response to stimulation is observed patients should similarly be advised to increase their steroid dose when appropriate. Continued very slow weaning of the exogenous glucocorticoids may be possible, but patients would require very close observation and monitoring including further stimulation testing. Full recovery of the endogenous HPA axis may take up to 12 months.

Conclusion
Reduction of glucocorticoids can be complicated by recurrence of the original disease or nonspecific symptoms that may represent adrenal suppression or steroid withdrawal syndrome. All individuals who have received a significant steroid dose for more than two weeks should be considered at risk of developing steroid-induced suppression of the HPA axis. Care must be taken to reduce the steroid dose slowly and formally test the axis when there is any doubt of its integrity.

References:

Declaration of interests
None to declare.

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