Is there a safe and effective way to wean patients off long-term glucocorticoids

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Abstract

Glucocorticoids are highly effective medicines in the treatment of inflammatory disorders. However they cause severe dose-related adverse reactions, particularly where taken systemically for prolonged periods. Systemic glucocorticoids are therefore given at dosage sufficient to control the disease, then withdrawn as fast as is possible to minimise dose-related adverse effects without losing disease control. End-of-use adverse reactions present a major challenge in the withdrawal of long term (>3 weeks) glucocorticoids. Suppression of the hypothalamic-pituitary-adrenal (HPA) axis causes adrenal insufficiency, which is potentially life threatening and can become symptomatic as treatment is withdrawn. Adrenal insufficiency can be extremely difficult to differentiate from 'glucocorticoid withdrawal syndrome', where patients experience symptoms despite adequate adrenal function, and from psychological dependence. Long term systemic glucocorticoids should therefore be withdrawn slowly. The rate at which the dose is tapered should initially be determined by treatment requirements of the underlying disease. Once physiological doses (prednisolone 7.5mg or equivalent) are reached, the rate of reduction is determined by rate of HPA recovery and need for exogenous glucocorticoid cover while endogenous secretion recovers. If symptoms prevent treatment withdrawal, HPA testing should be used to look for adrenal insufficiency. Patients with adrenal insufficiency require physiological doses of glucocorticoids for adrenal replacement, which may be lifelong if the HPA axis fails to recover.

Introduction

Glucocorticoids are commonly used for their anti-inflammatory and immunomodulatory properties in the treatment of a wide range of inflammatory, immunological, allergic and malignant diseases. A recent population study from Denmark found that the annual prevalence of systemic (oral and injectable) glucocorticoid use was ˜3%, increasing to 6.7-7.7% in people 60-79 years of age and to 9.7-11% in those [?]80 years of age [1]. In 2018 in England, 8 million prescriptions for systemic glucocorticoids, 21 million prescriptions for inhaled glucocorticoids and 12 million prescriptions for topical glucocorticoids were dispensed in the community [2]. Glucocorticoids bind to glucocorticoid receptors, which are expressed in almost every cell in the body and have pleiotropic effects on multiple signalling pathways [3]. This makes them highly effective anti-inflammatory drugs, but also causes diverse serious adverse effects that limit their use.

Adverse effects

Prolonged and/or high dose glucocorticoid therapy promotes gluconeogenesis, protein catabolism and lipolysis, reduces proliferation of actively dividing cells, promotes apoptosis, inhibits the synthesis of extracellular matrix proteins, has vasopressor effects and suppresses the hypothalamic pituitary axis [3]. Adverse effects of treatment therefore include weight gain, metabolic disorders, growth retardation and/or bone and muscle loss, poor wound healing, increased susceptibility to infection and adrenal insufficiency, as well as neuropsychiatric effects. Some toxicity from oral or injected glucocorticoids is inevitable, even with short courses of treatment. However, the adverse effects experienced by an individual depend on both the average and the cumulative dose of treatment, with harms experienced even at very low doses of glucocorticoids when given

over long periods of time (figure 1). This means that long term inhaled or topical glucocorticoids also have potential to cause systemic adverse effects. This is more likely for inhaled or topical glucocorticoids with greater potency (table 1) and is dependent on systemic bioavailability, which may be increased by a wide range of factors including drug-drug interactions and severity of underlying disease (figure 2).

Adrenal insufficiency . The endogenous glucocorticoid, cortisol is secreted by the adrenal cortex at around 5.7 mg/m^2/day [16], approximately equivalent to a therapeutic regimen of 15-25 mg hydrocortisone/day [17] or prednisolone 7.5 mg/day. Glucocorticoid release from the adrenal glands is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. In the hypothalamus, the circadian oscillator in the suprachiasmatic nucleus controls secretion of corticotrophin-release hormone (CRH) into hypophyseal portal veins. CRH stimulates the anterior pituitary gland to release stored adrenocorticotrophic hormone (ACTH) into the circulation and promotes synthesis of new ACTH. ACTH simulates cortisol secretion by the adrenal glands with a pronounced diurnal rhythm. Plasma cortisol concentrations peak at 06.00 to 07.00 am and reach a nadir at around 24.00 hours. Physiological and emotional stress override this daily rhythm, stimulating a rapid increase in cortisol levels. Cortisol exerts negative feedback on the hypothalamus and anterior pituitary gland, regulating secretion of CRH and ACTH. Exogenous glucocorticoids suppress the HPA axis by reducing secretion and synthesis of CRH and ACTH, which in turn reduces endogenous cortisol production and secretion by the adrenal glands. After a short course of exogenous glucocorticoids these changes can reverse rapidly [18]. However if treatment is prolonged, atrophy of corticotrophin cells in the anterior pituitary [19] and of the adrenal glands [20] may occur and reversal may be prolonged over weeks [21], months or years [22].

In a systematic review of studies measuring adrenal function following systemic glucocorticoid exposure, Joseph and colleagues found that a median of 37% (interquartile range 13-63%) patients had adrenal insufficiency [22]. Adrenal insufficiency occurred even with low dose (<5 mg prednisolone equivalent) and short duration (<4 weeks) glucocorticoid treatment and following tapered withdrawal. It persisted in 15% patients retested 3 years after glucocorticoid withdrawal. In a separate review, Broersen and colleagues found that there was no administration form, dosage, treatment duration or underlying disease for which adrenal insufficiency could be excluded, although increased dose and duration of treatment were associated with increased risk [23].

Challenges of glucocorticoid therapy

Glucocorticoid therapy has the potential for considerable benefit through control of life-threatening and/or disabling disease, but at the cost of considerable harms through dose-related and continuous use adverse reactions. The goal of glucocorticoid therapy is therefore to obtain the maximum possible therapeutic benefit at the lowest possible dosage, both average and cumulative, to minimise adverse effects. In practice, this is achieved by starting glucocorticoid treatment at a moderate to high dose (e.g. 40 mg prednisolone for an asthma exacerbation, 1000 mg methyl prednisolone for graft rejection reactions or relapse in multiple sclerosis) to gain disease control, then withdrawing glucocorticoid treatment to as low dose as can be achieved while still maintaining disease control. Glucocorticoid withdrawal is greatly complicated by the emergence of symptoms, which may be a manifestation of disease reactivation, an end-of-use adverse reaction caused by drug withdrawal (adrenal insufficiency, glucocorticoid withdrawal syndrome) or psychological dependence (figure 3). Distinguishing between these and supporting patients in successful withdrawal of glucocorticoids can be a considerable challenge.

Is there a safe and effective way to wean patients off long-term glucocorticoids?

Long term systemic glucocorticoid treatment can be defined as continuous treatment for more than 3 weeks. Long term glucocorticoids must be withdrawn slowly to prevent loss of disease control and manage end-of-use adverse reactions. This is usually done using a tapering regimen, an example used for patients with inflammatory rheumatic diseases is shown in table 2 [24]. This section discusses practical approaches to weaning patients off long term glucocorticoids that can help to minimise harms from loss of disease control and end-of-use adverse effects. These approaches are illustrated through discussion of 3 clinical cases shown in boxes 1-3.

Loss of disease control (Case study 1, box 1)

Effective treatment of chronic inflammatory disorders is essential to prevent long term structural changes and loss of function, such as joint destruction and loss of mobility in rheumatoid arthritis or airways remodelling and chronic breathlessness in asthma. Glucocorticoids are highly effective in the treatment of inflammation but their utility is limited by their dose-related and continuous use adverse effects. 'Steroid-sparing' strategies can be employed to improve the benefit: harm ratio of glucocorticoids. General principles include combining systemic glucocorticoids with topical glucocorticoids (e.g. intraarticular for arthritis, high dose inhaled for asthma) and/or with conventional and biological disease-modifying drugs (e.g. methotrexate or adalizumab for rheumatoid arthritis, omalizumab for asthma). A holistic approach should also include reviewing the diagnosis and need for glucocorticoids. For example a patient with 'asthma' who seems poorly-responsive to high dose glucocorticoids may actually have COPD, where systemic glucocorticoids are not usually indicated.

As glucocorticoid treatment is weaned, reactivation of disease may be difficult to distinguish from end of treatment adverse effects or re-emergence of symptoms of unrelated conditions. For example, a patient with rheumatic disease who complain of aches and pains as glucocorticoids are withdrawn may be experiencing reactivation of their inflammatory disease, 'pseudorheumatism' of glucocorticoid withdrawal, or renewed awareness of underlying osteoarthritis. These will affect the treatment taper in different ways. A disease flare may require an increase in glucocorticoid dose, although a relatively modest increase e.g. to the last effective dose in polymyalgia rheumatica [25], may be enough. Symptoms of glucocorticoid withdrawal syndrome or renewed awareness of underlying conditions can be managed with alternative therapies, such as non-steroidal anti-inflammatories for rheumatic symptoms. Slowing the taper may also allow glucocorticoid withdrawal symptoms to resolve.

Patient perception of glucocorticoids may affect their willingness to take treatment, with non-adherence leading to loss of disease control (Box 1). Anecdotally many patients starting glucocorticoid treatment express fears of weight gain, skin changes and 'becoming addicted' with one patient being particularly concerned because a relative had died from glucocorticoid-related adverse effects. These anecdotes are born out by studies of patient perceptions of glucocorticoid therapy, which found that patients voiced concerns about adverse effects [26] and, given a 'risk-free choice', preferred withdrawal of glucocorticoids over other agents [27]. It is essential that the benefits and risks of treatments and patient concerns are fully discussed before starting treatment and that the decision to undertake glucocorticoid treatment is made jointly by patient and practitioner.

Adrenal insufficiency (Case study 2, box 2)

Patients taking long term systemic glucocorticoids are at risk of HPA suppression. Where this has occurred, abrupt withdrawal of exogenous glucocorticoids or physiological stress such as intercurrent illness or surgery can cause life-threatening acute adrenal insufficiency. Although not all patients taking long term glucocorticoids develop adrenal insufficiency [22], it can be extremely difficult to distinguish those who do from those who don't. Potency, dose and duration of glucocorticoid treatment are imperfect predictors, patients may be asymptomatic even when therapy is withdrawn and blanket HPA testing is considered impractical. A general clinical approach therefore is to have a low threshold for suspecting HPA suppression in patients taking glucocorticoids and to require a gradual withdrawal of treatment for all those considered to have reached that threshold. Where treatment withdrawal is hampered by the emergence of symptoms (e.g. Case study 2, box 2), testing for HPA suppression can be useful to determine whether these are manifestations of adrenal insufficiency.

Suspecting HPA suppression

Small studies in healthy volunteers found that short (5-7 days) courses of high dose (40-50mg) prednisolone did not produce sustained HPA suppression [18, 28]. However, adrenal suppression was observed in steroid-naïve COPD patients after taking prednisolone 40 mg daily for 14 days. This persisted in some patients for at least 21 days [29]. Treatment cessation guidelines in the British National Formulary reflect this, identifying patients who have received more than 40 mg prednisolone (or equivalent) daily for more than week or who

have received glucocorticoid treatment for more than 3 weeks as requiring gradual treatment withdrawal [30].

Other patients who are likely to have HPA suppression secondary to glucocorticoid therapy include those who have been given repeat doses in the evening, have recently received repeat courses (particularly if longer than 3 weeks) and those who take a new short course of glucocorticoids within 1 year of stopping therapy [30].

The rate of treatment withdrawal in all patients is determined both by disease control and by suspicion of adrenal suppression. The rate of reduction from the initial treatment dose down to physiological doses (equivalent to prednisolone 7.5 mg) is determined by the treatment requirements of the underlying disease (e.g. table 2). The rate of reduction from physiological doses to zero is determined by the rate of HPA recovery and the need for exogenous glucocorticoid cover while endogenous glucocorticoid secretion recovers. After relatively short courses of glucocorticoids, HPA suppression can recover in days to weeks. However, where treatment duration has been long enough for adrenal atrophy to occur, recovery may take months to years or may not occur at all, necessitating long term adrenal replacement.

Testing for HPA suppression

HPA function testing is generally reserved for patients who become symptomatic when withdrawing from glucocorticoids. Its purpose is to distinguish adrenal insufficiency from glucocorticoid withdrawal syndrome (table 3). HPA function is tested by measurement of cortisol. Exogenous glucocorticoids interfere with the cortisol assay, so measurements must be made at least 12 hours after the last dose of hydrocortisone or 24 hours after the last dose of prednisolone. If this period without glucocorticoids is not achievable then treatment should be switched to an equivalent dose of dexamethasone (table 1) before testing as this does not interfere with the cortisol assay.

Patients should initially undergo measurement of 9am cortisol. Values of <100mmol/L indicate cortisol insufficiency and >450nmol/L indicate cortisol sufficiency. Where values are equivocal (100-449nmol/L), a stimulation test should be performed to measure cortisol before and at 30 and 60 minutes after administration of intramuscular synthetic ACTH (short synacthen test). A peak cortisol value of <550nmol/L after stimulation indicates cortisol insufficiency. Check all these reference values with your local laboratory as assays may vary.

Managing HPA suppression

Patients diagnosed with cortisol insufficiency require physiological glucocorticoid replacement with hydrocortisone 15-20 mg/day or prednisolone 4-5 mg/day. For some patients, very slow weaning of treatment from these doses over many months may allow full recovery of the HPA axis and eventual cessation of exogenous glucocorticoids. For other patients, recovery does not occur, and lifelong glucocorticoid replacement is required.

Patients with cortisol insufficiency are at risk of an adrenal crisis, particularly in times of intercurrent illness such as infection, trauma or surgery. They should be warned of the risk and advised to increase (double or treble) their glucocorticoid dose to a minimum of 40 mg hydrocortisone or prednisolone 10 mg if this occurs. Patients should be signposted to 'sick day rules guidance', such as that provided by the Addison's self-help group to help them with this [31].

Glucocorticoid dependence and withdrawal (Case study 3, box 3)

Glucocorticoid withdrawal syndrome is defined by symptoms that develop as glucocorticoid therapy is withdrawn, despite normal HPA function. These symptoms can be similar to those of adrenal insufficiency, which makes it difficult to tell the two conditions apart (table 3). One distinguishing feature is that glucocorticoid withdrawal syndrome can be symptomatic even at supraphysiological glucocorticoid doses, whereas adrenal insufficiency is controlled by physiological doses.

Inherent in the description of glucocorticoid withdrawal syndrome is the implication that patients become dependent on or 'addicted to' glucocorticoids, accounting for both physiological and psychological discomfort when treatment is withdrawn [32]. Glucocorticoids have pleiotropic effects, altering many different pathways and mediators, which could contribute to development of dependence. Candidates include CRH, vasopressin, pro-opiomelanocortin and the adrenergic system [33]. In the brain, exogenous glucocorticoids may alter neurotransmitters [32] and impair recovery from neuronal damage [7]. It is well recognised that patients taking glucocorticoids can develop neuropsychiatric effects including psychotic reactions, as well as changes in mood, cognition, memory and/or behaviour [7]. Neuropsychiatric effects including depression, delirium, confusion or disorientation, non-psychotic mania and panic disorder have also been reported during dose reduction [34] and may complicate treatment withdrawal. Glucocorticoids have been implicated as a driver of addictive behaviour [35] and occasionally are used as drugs of abuse [36]. Anfinson and colleagues identified 22 cases of glucocorticoid dependence on a MEDLINE search that met criteria for DSM I-IV substance dependence [36]. They commented that glucocorticoids may induce dependence through their propensity to induce euphoria and by directly influencing reward circuitry, as well as through physical dependence.

Managing glucocorticoid dependence

The physical and psychological effects of glucocorticoid withdrawal can make it difficult for patients to reduce the dose of their glucocorticoids. In case studies 2 and 3 this is illustrated by patients maintaining themselves on higher doses of glucocorticoids than those prescribed by their physicians. When discussing glucocorticoid tapering, patients should be counselled about the possibility of withdrawal symptoms. If these occur at supraphysiological doses of glucocorticoids, they can be managed by symptomatic treatments (e.g. non-steroidal anti-inflammatories for aches and pains) and by slowing the rate of glucocorticoid taper. If the symptoms are poorly tolerated, the dose of glucocorticoids can be increased to the lowest dose at which they are controlled and treatment tapered very slowly. If symptoms occur at or below physiological glucocorticoid doses, adrenal insufficiency must be excluded as described above. With time and a very slow treatment taper, glucocorticoid dependence may resolve. Where patients are unable to stop glucocorticoid therapy they should be maintained on the lowest possible dose of treatment. Some endocrinologists recommend switching from prednisolone to hydrocortisone if long term treatment is required because hydrocortisone appears to be associated with a lower risk of fractures [37].

Conclusion

Although glucocorticoids are effective anti-inflammatory drugs, long term use at even low doses has potential to cause harmful adverse reactions. A key principle of therapy is to use glucocorticoids at as low as dose and for as short a duration as possible to control disease to limit these adverse effects. However glucocorticoid withdrawal is also fraught with risk, including loss of disease control and end-of-use adverse effects, including the potential for life-threatening adrenal insufficiency. Steroid sparing strategies, glucocorticoid-tapering regimens and a low index of suspicion for HPA axis suppression are key to the safe and effective withdrawal of long term glucocorticoids.

BOX 1

Case study 1. Disease control

A 70-year-old woman experiences bilateral shoulder and hip pain and stiffness. She is diagnosed with polymyalgia rheumatica and commences treatment with prednisolone 15mg daily. After 3 weeks her symptoms have disappeared and she is advised to reduce her prednisolone dose to 12.5 mg for 3 weeks, then to 10 mg for 4 weeks, then by 1mg per month [25]. Three months later her concerned son tells her GP that she is fatigued and depressed and can't get out of bed or the bath. On enquiry she stopped her prednisolone after 6 weeks of treatment because of concerns about weight gain.

Discussion. Polymyalgia rheumatica (PMR) is an inflammatory musculoskeletal disorder of unknown aetiology, which classically responds well to systemic glucocorticoids. The treatment regimen described here is based on the recommendations of the British Society for Rheumatology and British Health Professionals in

Rheumatology [25] and is consistent with the example tapering regimen shown in table 2.

This patient stopped glucocorticoid treatment abruptly after 6 weeks of treatment. At this point rapid withdrawal could cause disease relapse or adrenal insufficiency. The systemic features of PMR e.g. fatigue, anorexia, fever, weight loss and depression can be difficult to distinguish from the symptoms of adrenal insufficiency. Raised inflammatory markers (C-reactive protein, erythrocyte sedimentation rate) would be supportive of disease reactivation. As she has now not had glucocorticoids for ˜9 weeks, one approach would be to recommence treatment for PMR at 15mg/day followed by the taper as planned. A key issue for this patient would be to discuss the benefits of the treatment in the context of her concerns about taking glucocorticoids to encourage her to adhere to treatment. Advice on avoiding weight gain with glucocorticoids could also be helpful (e.g. NHS guidance [38]). If she recommences glucocorticoid treatment, she should be advised not to stop prednisolone abruptly and provided with a steroid card.

BOX 2

Case study 2. End-of-use adverse reaction

A 64-year-old woman has taken prednisolone 10 mg daily for 6 months for rheumatoid arthritis, which is now well controlled by methotrexate. She is asked to reduce her prednisolone dose by 1mg/month with the aim of stopping the glucocorticoids. When she is reviewed 6 months later she is still taking prednisolone 10 mg daily. She managed to reduce the dose to 5mg daily using this regimen, but felt lethargic, nauseated and weak so returned to her usual dose.

Discussion

NICE guidelines indicate that long-term glucocorticoids should only be used for rheumatoid arthritis when all other disease-modifying treatment options have been offered and long-term complications have been fully discussed [39]. Short-term treatment may be considered for rapid control of inflammation in newly diagnosed rheumatoid arthritis or disease flares. For this patient, her arthritis is now controlled on methotrexate and withdrawal of treatment should be attempted.

When she tries to withdraw glucocorticoids, she develops symptoms that could be due to adrenal insufficiency or glucocorticoid withdrawal syndrome. The long duration of treatment and symptoms at a prednisolone dose below daily endogenous glucocorticoid secretion (˜7.5 mg prednisolone equivalent) increase the likelihood that she has hypothalamic-pituitary-adrenal (HPA) axis suppression and adrenal insufficiency. HPA axis testing is therefore indicated to determine her long-term management.

A reasonable approach for this patient would be to ask her to repeat the wean to prednisolone 5mg. She should then undergo measurement of 9am cortisol at least 24 hours after her last dose of prednisolone, which can otherwise interfere with the cortisol assay. If this test is equivocal (9am cortisol 100-449nmol/L), further testing with a short synacthen test will be required. Differentiating between adrenal insufficiency, which requires adrenal replacement, and glucocorticoid withdrawal syndrome, which may resolve if treatment is tapered very slowly, is important to direct therapy.

BOX 3

Case study 3. Psychological dependence

A 69-year-old man with advanced chronic obstructive pulmonary disease (COPD), anxiety and depression is seen by his GP to review the need for long term glucocorticoids. He takes prednisolone 20mg daily and feels unable to reduce the dose because of breathlessness. His weight has increased by 10kg in the past year, he has osteoporosis with a vertebral compression fracture and his random blood glucose is 12.3mmol/L.

Discussion

Long term systemic glucocorticoid therapy is not normally recommended for the treatment of COPD [40]. Some patients with advanced COPD may find it difficult to stop systemic glucocorticoids prescribed for

exacerbations, particularly where exacerbations are frequent. If patients cannot stop glucocorticoids, the dose should be kept as low as possible and the focus should be on preventing complications.

This patient feels breathless whenever he tries to reduce the dose of his prednisolone. There is little evidence that long-term systemic glucocorticoids improve lung physiology in people with stable COPD [41], so this may be due to 'psychological dependence' on glucocorticoids. A holistic approach would include: medical review to look for other causes of breathlessness; optimising COPD management (including smoking cessation, pulmonary rehabilitation and inhaler review); symptom management and psychological support. Glucocorticoids should be weaned in parallel to the lowest tolerated dose and measures to ameliorate the dose-related and continuous use adverse effects of osteoporosis (e.g. bisphosphonate treatment) and diabetes mellitus (e.g. low sugar diet, oral hypoglycaemic treatment) should be implemented to reduce the risks of future harm.

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Table 1. Relative potency of synthetic glucocorticoids

Corticosteroid	Routes of administration	Relative glucocorticoid receptor binding affinity	Systemic dosage equivalence	Potency classification when used topically at the concentrations (weight/volume) shown
Fluticasone furoate	Inhaled	2989		
Clobetasol proprionate	Topical			Very potent 0.05%
Fluocinolone Acetonide	Topical			Potent - 0.025% Moderate 0.00625%
Mometasone furoate	Inhaled, topical	2100		Potent 0.1%
Fluticasone propionate	Inhaled, topical	1775		Potent 0.05%
Beclomethasone dipropionate	Inhaled, topical	1345		Potent 0.025-0.05%
Betamethasone diproprionate	Oral, Topical			Potent 0.05%
Fludroxycortide	Topical			Moderate 0.0125%
Betamethasone valerate	Topical			Potent 0.1% Moderate 0.025%
Hydrocortisone butyrate	Topical			Potent 0.1%
Diflucortolone valerate	Topical			Very potent 0.3% Potent 0.1%

Corticosteroid	Routes of administration	Relative glucocorticoid receptor binding affinity	Systemic dosage equivalence	Potency classification when used topically at the concentrations (weight/volume) shown
Clobetasone butyrate	Topical			Moderate 0.05%
Ciclesonide (des-CIC)	Inhaled	1200		
Budesonide	Inhaled	935		
Triamcinolone acetonide	Inhaled	233	4mg	
Flunisolide	Inhaled	190		
Betamethasone sodium phosphate	Oral, injection		0.75mg	
Dexamethasone	Oral, injection	100	0.75 mg	
Methylprednisolone	Oral, injection		4 mg	
Prednisolone	Oral	12	5 mg	
Hydrocortisone	Oral, injection, topical	˜2.5	20 mg	Mild 0.1-2.5%

The table shows synthetic glucocorticoids administered systemically (oral or injection), topically and/or by inhalation ranked as far as possible from highest to lowest in terms of potency using glucocorticoid receptor binding affinity [4], systemic dosage equivalence [5] and topical steroid potency classification [6].

Table 2. An example tapering regimen for reducing glucocorticoid dose in patients with inflammatory rheumatic diseases [24]

Dose (prednisolone or equivalent)	Taper
>40 mg	5-10mg/day every 1-2 weeks
20-40mg	5mg/day every 1-2 weeks
10-20mg	2.5mg/day every 2-3 weeks
5-10mg	1mg/day every 2-4 weeks
<5mg	0.5mg/day every 2-4 weeks (can be achieved by alternating daily doses e.g. 5 mg on day 1, 4 mg on day 2 etc)

Table 3. Comparison of adrenal insufficiency and glucocorticoid withdrawal syndrome in patients withdrawing from long term glucocorticoids

	Adrenal insufficiency	**Glucocorticoid withdrawal syndrome**
Symptoms	anorexia, fatigue, nausea, vomiting, dyspnea, fever, arthralgia, myalgia, and orthostatic hypotension, dizziness, fainting, circulatory collapse	anorexia, nausea, emesis, weight loss, fatigue, myalgias, arthralgias, weakness, headache, abdominal pain, lethargy, postural hypotension, fever, skin desquamation, tachycardia, emotional lability, delirium, psychotic states
Steroid dosage	Symptomatic below physiological doses (prednisolone 7.5mg or equivalent)	Symptoms can occur at supraphysiological doses of glucocorticoids
HPA testing	Cortisol insufficiency 9am cortisol <100nmol/L and/or Peak cortisol after synacthen stimulation <550nmol/L	Normal HPA function 9am cortisol >450nmol/L and/or Peak cortisol after synacthen stimulation >550nmol/L
Risk of adrenal crisis	Yes	No
Management	Reduce glucocorticoids to physiological dose Long term replacement with hydrocortisone 15-20 mg/ day or prednisolone 4-5 mg/day Increase glucocorticoids during intercurrent illness Very slow wean over the long term to allow HPA axis recovery	Reduce glucocorticoids to the lowest possible dose that controls symptoms Then withdraw very slowly over months No need to increase glucocorticoids during intercurrent illness Consider retesting HPA axis if glucocorticoid wean is very prolonged and difficult

Figure legends

Figure 1. Adverse effects of glucocorticoids by dose and duration of treatment

The adverse effects of systemic glucocorticoids are plotted approximately at the earliest time after treatment initiation (in months) and the lowest dose (prednisolone equivalent) at which they have been reported to occur. For example, neuropsychiatric effects occur early in people taking high dose treatment whereas cardiovascular disease is not increased in people taking prednisolone unless the dose has been >7.5mg for >1 year. Even very low dose glucocorticoid treatment can cause adverse effects if taken over a long period of time.

Figure 2. Factors increasing the systemic bioavailability of glucocorticoids administered topically or by inhalation

Absorption of the drug from the site of administration is greater if drug molecules are lipophilic and soluble or formulated with a vehicle with solvent or occlusive properties, which increase epithelial permeability. It is also greater with higher dosage, application over greater surface area, and in underlying disease e.g. where there is inflammation increasing epithelial permeability.

In the plasma, glucocorticoids are bound to corticosteroid-binding globulin (transcortin) and albumin. Factors that reduce these proteins, such as disease states with increased protein loss or decreased synthesis, could increase free circulating glucocorticoids.

Interactions with drugs that inhibit the hepatic enzymes that clear glucocorticoids (e.g. cyclosporin, erythromycin, itraconazole and ritonavir) or induce hepatic enzymes that activate glucocorticoid prodrugs can increase systemic exposure to glucocorticoids. Systemic exposure is also increased if glucocorticoid clearance is reduced e.g. by hepatic or renal impairment, and by hypothyroidism and older age

Figure 3. Relationship of glucocorticoid dose to disease control and adverse drug reactions

At treatment doses of glucocorticoids, disease control comes at the cost of dose-related and continuous use adverse drug reactions. When glucocorticoids are withdrawn, disease reactivation and end-of-use (withdrawal) reactions emerge as dose-related adverse reactions diminish. Adrenal insufficiency can become symptomatic when the dose of exogenous glucocorticoids falls below physiological glucocorticoid levels. Psychological dependence on glucocorticoids is not dose dependent.

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