

Glucocorticoid Tapering: a Literature Review

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ABSTRACT

Glucocorticoids (GCs), a class of corticosteroids that widely used a variety of diseases, associated physiological processes in the body [1,2]. It has structurally and pharmacologically similar to the endogenous hormone cortisol with various beneficial functions like anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive effects. As an anti-inflammatory and immunosuppressive effect, corticosteroids through a combination of both inhibition & upregulation of gene transcription [3-5]. Despite beneficial effects, they also have side effects that depend on the dose, type of steroid and length of treatments [6]. Short courses of high-dose GCs usually are safe and reasonably well-tolerated, but they do have numerous potential adverse effects [7]. Many of the severe complications occur in long-term use at doses greater than 20 mg of prednisone per day for three weeks or more causes tertiary adrenal insufficiency due to the HPA-axis (Hypothalamic Pituitary Adrenal Axis) suppression by endogenous GCs [8-10]. In this article, we'll discuss how to manage GCs tapering and when is the right time to use GCs.

Keywords: corticosteroid, glucocorticoid, adrenal insufficiency, tapering

1. Introduction

GCs primarily used as potent anti-inflammatory effects in disorders of many organ systems. In the blood, the steroid bound to corticosteroid-binding globulin (CBG) as the stabilized protein. The intracellular receptor linked with stabilized protein, including heat shock protein 90 (Hsp90) and several others (X). When it binds a molecule of steroid, the associated bits are released. Complex steroid-receptor enters as a dimer in the nucleus links to the glucocorticoid response element (GRE) on the gene and regulates gene transcription. Protein that brings corticosteroid hormone is produced [11].

Despite beneficial effects, they also have side effects that depend on the dose, type of steroid, and length of treatments [6]. Short courses of high-dose GCs usually are safe and reasonably well-tolerated, but they do have numerous potential adverse effects [7,8]. However, long-term use of GCs is generally avoided, given the risk of severe acute complications such as infection, venous thromboembolism, avascular necrosis, and fractures, as well as chronic complications such as diabetes mellitus, hypertension, osteoporosis, and other features of iatrogenic Cushing's syndrome [12-16]. However, often overlook is the simultaneous suppression of endogenous HPA-axis, which

can last long after exogenous steroid therapy is stopped abruptly [17].

2. Discussion

As an anti-inflammatory and immunosuppressive effect, GCs through a combination of both inhibition & upregulation of gene transcription [3-5]. Repression of genes regulating expression of most inflammatory cytokines (IL-1 thru IL-6, IL-8, IL-10, IL-13, GM-CSF, TNF- α , Interferon- γ) and upregulation of the appearance of annexin A1 directly inhibits PLA2 (reduces prostaglandin & leukotriene production), inhibits COX-2, promotes neutrophil detachment from the endothelium and reduces neutrophil penetration through the endothelium of blood vessels [18]. An anti-proliferative effect exerts this effect by triggering cell apoptosis and inhibiting fibroblast proliferation [3-5].

2.1 Physiologic HPA Axis

GCs are hormones that are synthesized by the adrenal glands, where cortisol is the primary secretion. It was secreted by the anterior pituitary that controlled by an adrenocorticotropic hormone (ACTH), which in turn is regulated by corticotrophin-releasing hormone (CRH)

through a feedback mechanism (the less ACTH and CRH are released, the higher plasma cortisol concentration, and otherwise). The secretion of CRH and ACTH regulate by the feedback of cortisol at the level of the hypothalamus and pituitary. Endogenous cortisol production is equivalent to about 5-7 mg per m² per day equivalent to around 15-20 mg of oral hydrocortisone per day. During the physical and psychological stress levels, ACTH and cortisol are significantly increase mediated by CRH and vasopressin. The majority of circulating cortisol is bound to globulin (75–80%) and albumin (10–15%), leaving only 5–6% free to pass through cell membranes and initiate physiological responses [17]. The HPA axis secretes endogenous cortisol exhibits a circadian rhythm (Fig. 1). The highest concentrations of cortisol occur in the morning (at 6 and 8 am). It decreases during the afternoon (50% of the morning level by 4 pm) and reaching their lowest levels at around midnight [19-21].

Most cortisol use in clinical practice is synthetic brought about by modification of the underlying molecular structure to emphasize particular pharmacokinetic or pharmacodynamics attributes. Systemically GCs consist of short-acting, intermediate-acting, and long-acting (Table 1). In short-acting, cortisone is naturally metabolite of cortisol, when give systemically is converted in the liver to cortisol. In long-acting, hydrocortisone and betamethasone are the weakest and strongest GCs, respectively. Betamethasone and dexamethasone have long half-lives, and adverse effects can occur after the GC has been discontinued [8,17].

2.2 When of the Adrenal Suppression Occurs?

Side effects of GCs appear to be related to both the average dose and cumulative duration use [6]. Many of the severe complications occur in long-term use at doses greater than 20 mg of prednisone per day for three weeks or more causes tertiary adrenal insufficiency due to the HPA-axis (Hypothalamic Pituitary Adrenal Axis) suppression by endogenous GCs [8-10]. During the period which the axis takes to recover (12-18 months), the adrenal glands will not be able to make the GCs in sufficient quantities needed for daily physiology. It will not be able to increase GCs production to the level required during stress from three to ten times (for severe stress) daily production levels. This adjustment must be made through exogenous GC replacement and patient's education, until the patient documented to have the HPA axis recovered [24]. The onset of tertiary adrenal insufficiency is often very gradual, and it may go undetected. There are clinical features that include fatigue, muscle and joint pain, psychiatric symptoms and hyponatremia [25].

2.3 Management of Adrenal Suppression

There is limited evidence in the management of GCs tapering. Short-term GCs therapy (up to three weeks) can stop without tapering [26]. The goal of the taper is to use a rate of change that will prevent both repetitive activities of the underlying disease and symptoms of cortisol deficiency due to persistent HPA suppression with a decrement of 5 to 10 percent every one to four weeks while accommodating convenience and individual patient response [27-28]. A reduction dose needs in patients on long-term GC therapy. GCs dose slowly decreases to physiological dose over about 1 to 2 or more months and then discontinued after assessment of adrenal functions. Tests for recovery of adrenal functions may perform approximately every three months once the GC taper to physiological doses.

A tapered dose should not use if a patient has experienced significant side effects to low-dose steroids, or the other diseases were coexisting, which may be negatively affected by steroids. The adverse impact of GCs can limit by taking the following steps are used the lowest dose of GCs for the shortest period needed to achieve the treatment goals, management of preexisting comorbid conditions, and monitoring of patients under treatment for adverse effects [10,18].

Many RCTs have carried out regarding long-term GCs administration in long-term diseases such as rheumatoid arthritis (Table 3). GCs tapering was less successful in rheumatoid arthritis which shown from the success rate of therapy were 31 to 42 percent with 6,3 and 9,3 years of disease. No studies directly compared clinical outcomes in patients who tapered successfully versus unsuccessfully [25-26,30]. Beside tapering dosage, the best time to consume GCs should be when cortisol synthesis is not too high around 10 am to 9.00 pm (Fig.1) [31-32].

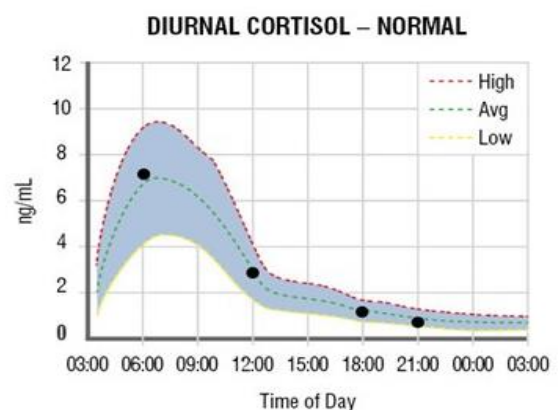


Figure 1. Circadian Rhythm of Cortisol [31-32].

Table 1 Classification of Glucocorticoid [6,20,21]

Active Drug	Approximate equivalent dose (mg)	Relative glucocorticoid activity	Relative mineralocorticoid activity	Duration of action (hours)	General therapeutic indication
Short-acting					
Hydrocortisone	20	1	1	8-12	Suitable for use in adrenal insufficiency
Cortisone	25	0,8	0,8	8-12	Similar to hydrocortisone
Intermediate-acting					
Prednisone	5	4	0,8	12-36	Suitable for long-term use
Prednisolone	5	4	0,8	12-36	Similar to prednisone
Methylprednisolone	4	5	Minimal	12-36	Anti-inflammatory /immunosuppressive
Triamcinolone	4	5	0	12-36	Anti-inflammatory /immunosuppressive
Long-acting					
Dexamethasone	0,75	30	Minimal	36-72	Used especially when water retention is undesirable
Betamethasone	0,6	30	Negligible	36-72	Similar to dexamethasone

Table 2. Guideline Recommendation of Glucocorticoid Tapering [26,29-30]

Article	Type of Disease	Recommendation
Dasgupta et al, 2010	Giant cell arteritis (GCA) or temporal arteritis	Continue prednisolone 40-60 mg (not < 0,75 mg/kg) for 4 weeks, then Reduction dose by 10 mg every 2 weeks to 20 mg, then Reduction dose by 2.5 mg every 2-4 weeks to 10 mg, then Reduction dose by 1 mg every 1-2 months, provided no relapse occurs
Robinson, 2014	Immune-related toxicity	Initiate corticosteroid taper over 3-6 weeks Reduction prednisolone dose by 10 mg every three days (as toxicity allows) until 10mg/day, then reduce by 5 mg every five days, then stop.
Furst & Saag, 2018	Rheumatoid	Initial dose above 40 mg/day of prednisone, reduction 5 to 10 mg/day every one to two weeks. If prednisone dose 20-40 mg/day, reduction 5 mg/day every one to two weeks. If prednisone dose 10-20 mg/day, reduction 2,5 mg/day every two to three weeks. If prednisone dose 5-10 mg/day, reduction 1 mg/day every two to four weeks.

Table 3 Description Of Randomized Trials Study Tapering Glucocorticoids (GCs) In Rheumatoid Arthritis [28]

	Boers et al, 1997	Hickling et al, 1998	Goekoop-Ruiterman, 2005	Tengstrand et al, 2007	Choy et al, 2008	Pincus et al, 2009
Study Design	Multicenter, parallel-group, double-blind, placebo-controlled	Multicenter, double-blind, placebo-controlled	Multicenter, 4-arm active-controlled, blinded assessor	Single-center, placebo-controlled	Multicenter, factorial, double-blind, placebo-controlled	Single-center, double-blind, placebo-controlled
Initial daily oral GC dose, mg	Prednisolone 60	Prednisone 7,5	Prednisone 60	Prednisolone 5-7,5	Prednisolone 60	Prednisone 1-4
Taper protocol	Weeks 1-6: weekly decrease by 20-38% Weeks 7-28: 7,5 mg daily Week 29-34: 1 day no GCs for 1st week then 2 days	7,5 mg every other day for 2 wks, then every third day for 2 wks, then discontinued	Decrease to 7,5 mg daily over 7 weeks	Decrease in total weekly dose ease 2,5 mg once a week	Decrease to 7,5 mg at 6 weeks; Week 6-28: 7,5 mg daily; Week 29-34: tapered at an undefined rate	Decrease by 1 mg every 4 wks
Duration of GC, weeks	35	4	28	Up to 52	34	16
Successfully taper GC	71 (92)	31 (86)	104 (78)	11 (42)	NP	5 (31)

Conclusion

Tapering dosage is needed when administering in long-term corticosteroids. It has given to avoid the occurrence of HPA axis suppression that occurs after administration for three weeks in adults. Beside tapering dosage, the best time to consume GCs should be when cortisol synthesis is not too high around 10 am to 9.00 pm.

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