Oral Diseases (2006) 12, 436–442. doi:10.1111/j.1601-0825.2006.01290.x

http://www.blackwellmunksgaard.com

INVITED REVIEW

Therapeutic doses of glucocorticoids: implications for oral medicine

SK Baid, LK Nieman

Reproductive Biology and Medicine Branch, National Institute of Child Health and Development, National Institutes of Health, Bethesda, MD, USA

Glucocorticoids can cause adverse systemic side-effects ranging from iatrogenic Cushing's syndrome during treatment, to hypothalamic–pituitary–adrenal axis suppression and clinically significant adrenal insufficiency when the agents are discontinued. While the oral route of administration is most often implicated, it is now becoming more apparent that inhaled and topical administration also can cause these effects. Given the high therapeutic value of glucocorticoids, the ability to prescribe these agents while maintaining a low risk-to-benefit ratio for patients is critical. The aim of this review is to provide oral healthcare practitioners with a practical guide to commonly used glucocorticoids, their adverse effects, and perioperative use.
Oral Diseases (2006) **12**, 436–442

Keywords: glucocorticoids; adrenal insufficiency; inhaled corticosteroids; steroid supplementation; hypothalamic--pituitary--adrenal axis

Introduction

It is estimated that up to 1% of the adult population in the US and UK receive prescriptions for glucocorticoids each year (Feldstein *et al*, 2005). The increasing use of glucocorticoid therapy for many inflammatory and autoimmune diseases has increased the prevalence of significant iatrogenic adverse effects. In the field of oral medicine, of most concern are local adverse effects and the possibility of hypothalamic–pituitary–adrenal (HPA) axis suppression resulting in clinical adrenal insufficiency when the glucocorticoids are discontinued. This article will review HPA axis physiology, types of glucocorticoid therapy, local and systemic adverse effects of glucocorticoid therapy, and perioperative glucocorticoid supplementation guidelines as relevant to oral diseases.

Correspondence: Lynnette K Nieman, Building 10, CRC 1E-3140 MSC 1109, 10 Center Drive, Bethesda, MD 20892-1109, USA. Tel: 301-496-8935, Fax: 301-402-0884, E-mail: niemanl@nih.gov
Received 19 April 2006; accepted 23 April 2006

Hypothalamic–pituitary–adrenal axis physiology

Before going further, it is important to define terms that will be used throughout this review and to describe the physiology related to cortisol production and action. The term 'glucocorticoid' refers to steroid hormones, both endogenous and exogenous, that bind to the glucocorticoid receptor and cause clinical glucocorticoid effects. Glucocorticoids act on nearly all cells in the body. They stabilize the vasculature, increase glucose availability and suppress the immune system. Cortisol is the most important glucocorticoid in humans.

The hypothalamus and pituitary gland regulate adrenal glucocorticoid production, forming the HPA axis. Corticotropin-releasing hormone (CRH) from the hypothalamus stimulates pituitary secretion of corticotropin (ACTH), which then stimulates adrenal production and release of cortisol. Once a physiologic set point of cortisol is reached, CRH and ACTH secretion are decreased via cortisol-negative feedback at the CRH neuron and pituitary corticotrope. In healthy people, circulating cortisol levels follow a diurnal rhythm, with highest values just before waking, and lowest values at or around bedtime. Plasma cortisol concentrations vary considerably during the day because of this normal physiologic diurnal rhythm and the pulsatile nature of cortisol secretion. Plasma cortisol concentrations also vary according to a person's mental and physical state of being. Emotional states (excitement, fear), pain, trauma, illness, and food ingestion are associated with increased circulating cortisol levels.

Exogenous glucocorticoids can suppress the HPA axis via negative feedback at the hypothalamus and pituitary gland, so that clinical adrenal insufficiency may result when the agents are discontinued. Symptoms of chronic adrenal insufficiency include lethargy, malaise, nausea, anorexia, weight loss, and dizziness. Patients also may show signs of hypoglycemia, and less commonly,

hyponatremia or hypotension. Acute adrenal insufficiency or 'crisis' is marked by nausea, vomiting, fever, hypotension, dehydration and the aforementioned laboratory abnormalities.

The term 'mineralocorticoid' refers to steroid hormones that bind to the mineralocorticoid receptor to regulate salt and water metabolism and help maintain intravascular pressure. Aldosterone, the most important mineralocorticoid in humans, causes sodium and water conservation and potassium excretion. Synthetic mineralocorticoids are rarely administered in doses that affect the mouth, and are not discussed further.

Glucocorticoid therapy

Glucocorticoids are formulated as oral, intravenous, inhaled, nasal, topical, and intra-articular preparations. Regardless of the route of administration, glucocorticoids can cause systemic adverse effects if absorbed into the circulation. Unfortunately, there is no absolute dose threshold at which adverse effects will not occur. While the type of glucocorticoid, dose and duration of treatment provide a rough guide to the probability of adverse side-effects, there is considerable inter-individual variability in this regard. The mechanism(s) behind this variability is unknown.

Adverse systemic glucocorticoid effects include but are not limited to HPA axis suppression, and Cushingoid features such as easy bruising, thinning of skin, truncal obesity, hypertension, hyperglycemia, mood changes (including anxiety, depression and psychosis), decreased libido, irregular or absent menses, purple striae, impaired wound healing, proximal muscle weakness, subcapsular cataracts, pro-thrombotic coagulopathy and decreased bone mineral density. Cognitive dysfunction such as decreased attention span, forgetfulness, and inability to concentrate can also occur.

Oral systemic glucocorticoids

The most commonly used synthetic oral glucocorticoid preparations are hydrocortisone, prednisone, dexamethasone, and cortisone acetate. Hydrocortisone, the exogenous chemical equivalent of endogenous cortisol, is converted to the active hormone in the liver. The bioavailability after oral administration of glucocorticoids is 60–100% (Czock *et al*, 2005). Each drug is characterized by a specific half-life, glucocorticoid potency and mineralocorticoid activity (Table 1). Oral formulations are more likely to cause adverse systemic effects compared with inhaled, topical or intra-articular glucocorticoids because more drug reaches the systemic circulation.

The risk of adrenal insufficiency caused by oral agents correlates roughly with glucocorticoid potency, biologic half-life, daily dose and duration of plasma ACTH suppression after a single dose (Krasner, 1999). Dexamethasone has the longest effect on ACTH suppression, while hydrocortisone and cortisone acetate are the least suppressive drugs (Axelrod, 1976).

It is generally accepted that adrenal insufficiency caused by HPA axis suppression is more likely to occur when steroid doses equivalent to 20–30 mg day^{-1} of prednisone given for longer than 1 week are discontinued (Axelrod, 1976). Similar daily doses given for <1 week may cause slight and transient HPA axis suppression; however, it is unlikely that clinically significant adrenal insufficiency results.

Inhaled corticosteroids

Inhaled corticosteroids are the standard of care for many asthmatic patients and represent one of the most common uses of glucocorticoids.

Local adverse effects of inhaled corticosteroids include pharyngitis, dysphonia, reflex cough, bronchospasm and oropharyngeal candidiasis. The most common problems, affecting up to 40% of patients, are dysphonia and hoarseness caused by drug deposition into the larynx. Oropharyngeal candidiasis occurs in approximately 5% of patients (Barnes, 2006). Local adverse effects can be reduced by use of a large volume spacer device and/or mouth rinsing, either with water or a prescribed mouthwash (Ellepola and Samaranayake, 2001).

The presence and severity of systemic adverse side-effects caused by inhaled corticosteroids depends on how much drug reaches the circulation. The proportion of inhaled corticosteroid delivered to the lung and gastrointestinal tract reflects the delivery device, drug formulation, and patient-specific factors. Most dry powder inhalers, nebulizers and pressurized metered dose inhalers (with spacers) deliver only 10–20% of the dose to the airways with the remainder of drug being deposited into the oropharynx (Gulliver and Eid, 2005). Drug deposited into the oropharynx does not reach the systemic circulation as it is swallowed and undergoes first pass metabolism. In contrast, there is no evidence of metabolic inactivation of inhaled corticosteroids in the lung, allowing the dose reaching the airways to be

Table 1 Glucocorticoid equivalencies after oral administration[a]

Name	*Biologic half-life (h)*	*Glucocorticoid potency*	*Mineralocorticoid activity*	*Adult physiologic replacement dose (mg)*
Hydrocortisone	8–12	1	2	20
Cortisone acetate	8–12	0.8	2	25
Prednisone	18–36	4	1	5
Prednisolone	18–36	4	1	5
Dexamethasone	36–54	25–50	0	0.5
Fludrocortisone	18–36	15	150	0.05–0.2

[a]Adapted, with permission from Yaffe SJ, Aranda JV, eds (Liapi and Chrousos, 1992).

absorbed into the systemic circulation (Lipworth, 1999; Gulliver and Eid, 2005).

The relative systemic activity of inhaled corticosteroids has been best assessed by cortisol suppression. Listed from highest systemic activity to lowest systemic activity, they are: fluticasone propionate = mometasone furoate > budesonide = beclomethasone dipropionate > triamcinolone acetonide = flunisolide (Gulliver and Eid, 2005).

Dose-related adrenal axis suppression by inhaled corticosteroids has been the subject of many studies. Todd *et al* (2002) retrospectively reviewed the frequency of acute adrenal crisis associated with inhaled corticosteroid use. They found that 33 of 2912 patients met the diagnostic criteria for acute adrenal crisis, 28 children and five adults; 30 of these patients received fluticasone propionate, which, as noted above, has high relative systemic availability. In most of these cases the doses of inhaled corticosteroids were high; however, they did not exceed the accepted treatment guidelines for severe persistent asthma (Todd *et al*, 2002).

In contrast, Brown *et al* (1991) conducted two small studies showing that other inhaled corticosteroids have a less significant suppressive effect on the HPA axis. In the initial cross-sectional study, 62 of 78 patients on long-term high dose (1.2–2.6 mg day^{-1}) budesonide or beclomethasone dipropionate did not show evidence of suppression based on morning plasma and 24-h urine cortisol levels or the cortisol response to 250 μg Cortrosyn (see below for testing approaches). In the remaining patients, HPA axis suppression correlated with duration of treatment and history of systemic steroid use (Brown *et al*, 1991).

In a second prospective study, 24 patients presenting to the emergency room with an acute severe asthma exacerbation had plasma cortisol levels drawn at the time of evaluation. Patients had received inhaled budesonide and beclomethasone dipropionate treatment for 2–16 years. None had recent or current use of oral systemic corticosteroids. Of 13 patients on high doses of inhaled corticosteroids (1.5–2.4 mg day^{-1}) four did not show a normal HPA axis response to the stress of the asthma exacerbation. Two of seven steroid-naïve patients and three of four patients on medium dose (0.6–1.2 mg day^{-1}) also failed to mount a normal HPA axis response (Brown *et al*, 1992). It should be noted that fluticasone propionate was not evaluated in these studies.

In a meta-analysis of systemic adverse effects of inhaled corticosteroids, Lipworth (1999) reported that marked adrenal suppression occurs with doses of inhaled corticosteroid (budesonide, beclomethasone dipropionate, triamcinolone acetonide) above 1.5 mg day^{-1} (0.75 mg day^{-1} for fluticasone propionate). The duration of high dose inhaled corticosteroid treatment after which a patient is at greatest risk for HPA axis suppression is not known. Unfortunately, most studies evaluating inhaled corticosteroids and HPA axis suppression have been limited by lack of control subjects, lack of consideration of previous oral glucocorticoid therapy, inclusion of different duration of treatment, type of inhaler, and method of HPA axis assessment (Dahl, 2006). Although less likely to cause adrenal insufficiency than oral systemic preparations, the studies cited above indicate that adrenal insufficiency is a real consequence of inhaled corticosteroid therapy, and HPA axis evaluation may be warranted.

Inhaled corticosteroids are associated with other systemic adverse effects such as reduced growth velocity, decreased bone mineral density, and excessive skin thinning and bruising. They have also been implicated in an increased risk of subcapsular cataracts and glaucoma (Lipworth, 1999; Dahl, 2006). Specific to oral diseases, the association between inhaled corticosteroids and bone metabolism is of particular importance.

Some studies show that use of long-term inhaled corticosteroids is associated with decreased bone mineral density in the distal radius, hip and spine (El *et al*, 2005; Dahl, 2006). Komerik *et al* (2005) in a cross-sectional study, found that bone mineral density of the mandible was significantly lower in 30 patients receiving long-term inhaled corticosteroids when compared with 30 healthy subjects. While decreased bone mineral density of the mandible may increase the risk of tooth loss, no significant relationship between the two was found in this small study. By contrast, Walsh *et al* (2001) found that patients taking oral corticosteroids were more likely to have fewer natural teeth or teeth in poor condition. The authors comment that inhaled corticosteroids may have contributed to this condition in some of their patients.

There also is concern that inhaled corticosteroid use in children may increase the risk of dental caries. Wogelius *et al* (2004) conducted a cohort study of approximately 5000 children taking one or more asthma drug prescriptions, including inhaled β_2 agonists, oral β_2 agonists and/or inhaled corticosteroids. Although they found an increased risk of caries in permanent teeth in these patients, it is possible that asthma itself causes an increased risk of dental caries. In addition, most patients were on combination therapy of inhaled β_2 agonists and inhaled corticosteroids, so that glucocorticoids *per se* could not be implicated.

A relatively new inhaled corticosteroid, ciclesonide, may have a more favorable adverse effect profile. This agent is unique in that it is not a halogenated compound, unlike other available inhaled corticosteroids. Halogenation slows drug metabolism and increases systemic bioavailability (Gulliver and Eid, 2005). Ciclesonide is metabolized in the lungs to the active compound, desisobutyryl-ciclesonide. It has favorable pharmacokinetic characteristics, such as low oral bioavailability, rapid clearance, and extensive binding to serum proteins, which limit systemic exposure and, thus, adverse side-effects (Sfzeler *et al*, 2005). Ciclesonide does not have a significant suppressive effect on the HPA axis. There are no published studies looking at the association of ciclesonide with the development of other systemic adverse effects of cortisol excess, although, this is unlikely given the drug's low systemic bioavailability. If further studies confirm this favorable side-effect

profile, ciclesonide may become the optimal agent for inhaled corticosteroid therapy.

Intranasal corticosteroids
Intranasal corticosteroids are one of the most effective medications for the treatment of allergic rhinitis. Currently available preparations include beclomethasone, budesonide, flunisolide, fluticasone propionate, mometasone, triamcinolone, and ciclesonide. Local adverse effects include irritation of the nose and throat, sneezing bouts, crusting of the nasal mucosa, transient dryness, minor epistaxis and rarely, ulceration (Salib and Howarth, 2003). Again, systemic adverse effects are related to the amount of drug reaching the circulation, which is influenced by delivery device, drug formulation and patient-specific factors. The newer intranasal corticosteroids (fluticasone propionate, budesonide, triamcinolone, and mometasone) can be used effectively at lower doses, have extensive hepatic first pass metabolism and limited systemic bioavailability. Patients using only these agents are at low risk for developing HPA axis suppression and do not appear to develop other adverse systemic effects (Salib and Howarth, 2003). It is those patients taking nasal corticosteroids in addition to other glucocorticoid therapy who may be at risk of developing systemic adverse effects (Gulliver and Eid, 2005).

Topical steroids
Many vesiculo-erosive oral mucosal diseases are treated with topical corticosteroids. There is limited published information regarding HPA axis suppression resulting from this route of administration. However, after review of unpublished, open label studies in children, an FDA advisory committee concluded that both high and medium potency agents were associated with HPA axis suppression (eFacts, Facts and Comparison 4.0 website: http://online.factsandcomparisons.com/ and USPDI Updates On-line, Vol. 1: http://www.micromedex.com/cust_center/cs-uspup.htm).

Systemic absorption of any topical steroid, whether from the skin or the oral mucosa, increases when the skin surface is not intact. Patients with large erosive or atrophied areas and/or the presence of open blood vessels on ulcerated surfaces have a greater likelihood of systemic adverse effects. As with other modes of delivery, factors that influence HPA axis suppression and adverse effects from topical steroids include the type of steroid, dose, vehicle of administration, and individual susceptibility. In the mouth, aqueous rinses expose more of the oral mucosa and prolong the contact between drug and lesion compared with gels (Gonzalez-Moles and Scully, 2005).

The judicious use of topical corticosteroids diminishes the risk of adverse effects. An unnecessarily high potency or concentration should not be prescribed. Aqueous oral solutions should be avoided if possible. Alternate day therapy should be considered as the patient's disease comes under control (Gonzalez-Moles and Scully, 2005). Patients with disease not responding to steroid therapy should be reevaluated to ensure that the diagnosis is correct prior to increasing the dose and/or potency of therapy (Gonzalez-Moles and Scully, 2005). Close monitoring of the patient is essential for the recognition and prevention of unnecessary long-term systemic adverse effects.

Intra-articular steroid preparations
Intra-articular steroid preparations infrequently cause clinically significant adrenal insufficiency. The risk of HPA axis suppression increases with multiple or frequent injections or high doses. This form of therapy will not be discussed further in this review.

Perioperative coverage

Supplemental perioperative glucocorticoid coverage for patients who are glucocorticoid dependent or who may have HPA axis suppression is a controversial area. In the 1950s and 1960s, reports of death secondary to adrenal crisis led to the current practice of treating glucocorticoid-dependent patients with high doses of steroids before and after surgery without evaluation of the HPA axis. Today, the typical dose of hydrocortisone given perioperatively for any surgery is 200–300 mg day^{-1} (Coursin and Wood, 2002). However, except in patients undergoing surgeries classified as 'major stress,' current guidelines (below) recommend lower doses of glucocorticoids.

The physiologic rates of cortisol production in healthy individuals and stressed patients have been used to justify increased perioperative glucocorticoid administration. In healthy people, daily cortisol production rates range from 5 to 10 mg m^{-2} day^{-1} (Esteban *et al*, 1991; Brandon *et al*, 1999). Kehlet reports that the daily cortisol production rises to 50 mg/24 h in patients undergoing minor surgeries and up to 75–150 mg/24 h for patients undergoing major surgeries (Kehlet, 1975). Cortisol levels return to baseline within 24–48 h after surgery (Kehlet, 1975).

In patients with presumed or biochemically confirmed HPA axis suppression secondary to exogenous glucocorticoids, it is reasonable to think that perioperative glucocorticoid coverage should correspond to the amount of glucocorticoid normally secreted during surgery. However, a few studies have shown that supplemental coverage may not be needed in all glucocorticoid-dependent patients. In a double-blind randomized controlled trial, Glowniak and Loriaux (1997) studied perioperative glucocorticoid coverage in 18 patients undergoing 'moderate stress' surgeries such as splenectomy, total knee arthroplasty and Nissen fundoplication. Patients had biochemically confirmed adrenal insufficiency caused by prednisone-induced HPA axis suppression and were randomly assigned to receive perioperative glucocorticoids or normal saline and their usual dose of prednisone. One patient in the placebo group experienced intra-operative hypotension that responded well to volume replacement. A second patient, in the glucocorticoid treatment group, experienced both intra- and postoperative hypotension, which was thought to be caused by excess opioid administration and inadequate volume replacement. This study

Table 2 Perioperative corticosteroid supplementation for oral healthcare procedures

Current daily dose of prednisolone	*Supplementary steroid cover required*
10 mg	Assume normal HPA response. Usual preoperative steroids, no supplementary steroid cover required
>10 mg	Simple surgery under local anesthesia (e.g. single extraction, gingivectomy): usual preoperative steroids. No supplementary steroid cover required Minor surgery (e.g. surgical extractions or multiple extractions): usual preoperative steroids; 25 mg hydrocortisone intravenously before surgery at induction of anesthesia Moderate surgery (e.g. mandible/zygoma): usual preoperative steroids; 25 mg hydrocortisone intravenously at induction plus 100 mg day^{-1} intravenously over 24 h[a] Major surgery (e.g. head and neck/orthognathic surgery): usual preoperative steroids; 25 mg hydrocortisone intravenously plus 100 mg day^{-1} intravenously for 48–72 h[a] Patients who have not received steroids for more than 3 months require no perioperative supplementation

Reproduced from Dental Update (ISSN 0305-5000), with permission from George Warman Publications (UK) Ltd, Guildford, UK.
[a]Continuous infusion.

points out that glucocorticoid supplementation beyond the routine daily dose may not be necessary to prevent hemodynamic compromise in the perioperative period (Glowniak and Loriaux, 1997).

Kehlet and Binder (1973) also reported that volume-responsive bleeding and sepsis, and not adrenal insufficiency, caused most cases of postoperative hypotension in at-risk patients. Thus, the general fear of inducing adrenal crisis in these patients is likely unfounded and the prescription of glucocorticoid supplementation may not always be necessary.

Salem *et al* (1994) reviewed the literature on perioperative glucocorticoid coverage and developed guidelines for glucocorticoid-dependent patients. These recommendations were based on presumed activation of the adrenal axis as a result of surgical stress as well as cortisol production rates. There are no controlled clinical trials supporting these recommendations.

For minor surgical stress (e.g. inguinal herniorrhaphy), glucocorticoid coverage of a 25 mg hydrocortisone dose equivalent (enteral or parenteral) on the day of surgery is recommended. If the patient's maintenance steroid dose is the equivalent of 25 mg hydrocortisone, no further coverage is necessary.

For moderate surgical stress (e.g. non-laparoscopic cholecystectomy, lower extremity revascularization, total joint replacement) a 50–75 mg hydrocortisone dose equivalent is recommended. The patient should take his/her maintenance dose preoperatively followed by intravenous hydrocortisone 50–75 mg in divided doses (i.e. every 8 h) beginning intraoperatively and continuing 24 h postoperatively and return to his/her preoperative dose (enteral or parenteral) on postoperative day 2.

For major surgical stress (e.g. cardiac surgery, pancreatoduodenectomy, esophagogastrectomy, total proctocolectomy), a 100–150 mg hydrocortisone dose equivalent is recommended. The patient should take his/her maintenance dose preoperatively, followed by hydrocortisone 100–150 mg in divided doses beginning intraoperatively and continuing intravenously for 48–72 h postoperatively. The glucocorticoid dose should be rapidly tapered to the patient's preoperative dose provided that the patient has not suffered other medical complications, in which case further evaluation of steroid dosing would be required (Salem *et al*, 1994).

Additional guidelines have been proposed for dental procedures. Key *et al* (2003) have adapted the above perioperative glucocorticoid recommendations to better meet the needs of oral healthcare providers (Table 2).

Which patients require HPA axis testing?

Given the number of patients receiving glucocorticoids, the question often arises, 'Who needs HPA axis evaluation before a procedure?' For the majority of patients on physiologic replacement doses of steroids, further HPA axis evaluation is unnecessary. The perioperative glucocorticoid supplementation guidelines above can be followed.

Most patients on supraphysiologic doses of steroids (equivalent of prednisone 20–30 mg > 5 days) will have HPA axis suppression. The key is to compare the patient's daily glucocorticoid dose to the dose recommended for his/her specific surgery. A general rule to follow is that if the recommended surgical dose is less than or equal to the patient's daily dose, no further supplementation is necessary. If the patient's daily dose is less than the recommended surgical dose, then, supplementation according to the above guidelines is appropriate and HPA axis testing is not needed. It is those patients in whom corticosteroid therapy has been discontinued recently or who are on high doses of inhaled or topical oral corticosteroids who may need further evaluation.

Evaluation of the HPA axis

The available methods to evaluate the hypothalamic pituitary adrenal axis are listed in Table 3.

An unstimulated morning serum cortisol measurement is most helpful when the value obtained is extremely low or normal (>18 $\mu g\ dl^{-1}$). There are data to support that a morning serum cortisol level of ≤ 3 $\mu g\ dl^{-1}$ is diagnostic of adrenal insufficiency. It is accepted that a level >18 or 19 $\mu g\ dl^{-1}$ represents

Table 3 Evaluation of the hypothalamic–pituitary–adrenal axis

Test	*Validated test for adrenal insufficiency?*	*Tests entire HPA axis?*	*Tests adrenal cortisol synthesis*	*Conveniences /drawbacks*
AM serum cortisol	Yes	Yes	Yes	Often indeterminate
24 h urine free cortisol	No	Yes	Yes	N/A
Salivary cortisol	No	Yes	Yes	N/A
1 μg Cortrosyn test	Yes	Yes	Yes	Dose formulation challenging
250 μg Cortrosyn test	Yes	No	Yes	Familiarity amongst physicians and pharmacies
Metyrapone test	Yes	Yes	Yes	Metyrapone is difficult to obtain in USA
Insulin tolerance test	Yes	Yes	Yes	Has risk; not performed by most physicians

adrenal sufficiency (Grinspoon, 1994). However, for intermediate values, the test is indeterminate and another form of evaluation must be employed.

In the US, the 250 μg Cortrosyn (synthetic ACTH) stimulation test is the most commonly used test for evaluation of adrenal insufficiency. It is minimally invasive, requiring intravenous access and blood draws. It is performed by drawing a baseline serum cortisol level, which is immediately followed by intravenous injection of Cortrosyn, 250 μg. Blood is drawn 30 and 60 min later for measurement of cortisol. Serum cortisol values of $\geq$18 μg dl^{-1} at any time-point are consistent with adrenal sufficiency (Speckart *et al*, 1971; May and Carey, 1985).

One drawback of the Cortrosyn stimulation test is that it only indirectly tests the integrity of the hypothalamus and pituitary gland. When CRH or ACTH secretion decrease, it takes up to 6 weeks for the adrenal glands to atrophy and significantly decrease cortisol production in response to the 250 μg pharmacologic Cortrosyn dose. Thus, if a patient has recent onset of hypothalamic or pituitary disease and is tested before the adrenal glands have atrophied, the result may be falsely normal. Therefore, it is important to consider the length of time between discontinuation of glucocorticoids and HPA axis testing as one decides on glucocorticoid replacement or perioperative coverage.

The 1 μg Cortrosyn stimulation test, metyrapone test and insulin tolerance test also are used to diagnose adrenal insufficiency; however, each test has limitations which preclude its use for routine testing (Nieman, 2003).

Conclusion

Given the increasing use of glucocorticoids in the treatment of anti-inflammatory and immune-mediated diseases, one must be aware of potential local and systemic adverse effects. Regular evaluation and titration of glucocorticoid dose to the lowest effective dose possible will help to reduce the incidence of local and systemic adverse effects of this therapy. The presence of physical signs and symptoms of glucocorticoid excess should prompt HPA axis testing if glucocorticoids will be discontinued. However, HPA axis suppression may be the only adverse effect of glucocorticoid therapy. The type of glucocorticoid, route of administration and cumulative dose and duration of treatment provide a rough guide as to which patients should be evaluated for adrenal insufficiency. Conservative use of glucocorticoid supplementation perioperatively should be strongly considered along with the previously published recommendations for surgical and dental procedures.

Acknowledgement

This work was supported by the intramural program of NICHD, NIH.

References

Axelrod L (1976). Glucocorticoid therapy. *Medicine (Baltimore)* **55:** 39–65.

Barnes PJ (2006). Corticosteroid effects on cell signaling. *Eur Respir J* **27:** 413–426.

Brandon DD, Isabelle LM, Samuels MH, Kendall JW, Loriaux DL (1999). Cortisol production rate measurement by stable isotope dilution using gas chromatography-negative ion chemical ionization mass spectrometry. *Steroids* **64:** 372–378.

Brown PH, Blundell G, Greening AP, Crompton GK (1991). Hypothalamo-pituitary-adrenal axis suppression in asthmatics inhaling high dose corticosteroids. *Respir Med* **85:** 501–510.

Brown PH, Blundell G, Greening AP, Crompton GK (1992). High dose inhaled steroid therapy and the cortisol excess response to acute severe asthma. *Respir Med* **86:** 495–497.

Coursin DB, Wood KE (2002). Corticosteroid supplementation for adrenal insufficiency. *JAMA* **287:** 236–240.

Czock D, Keller F, Rasche FM, Haussler U (2005). Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet* **44:** 61–98.

Dahl R (2006). Systemic side effects of inhaled corticosteroids in patients with asthma. *Resp Med* [ePub Ahead of print]. doi: 10.1016/j.rmed.2005.11.020.

El O, Gulbahar S, Cevlan E *et al* (2005). Bone mineral density in asthmatic patients using low dose inhaled glucocorticosteroids. *J Invest Allergol Clin Immunol* **15:** 57–62.

Ellepola AN, Samaranayake LP (2001). Inhalational and topical steroids, and oral candidosis: a mini review. *Oral Dis* **7:** 211–216.

Esteban NV, Loughlin T, Yergey AL *et al* (1991). Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *J Clin Endocrinol Metab* **71:** 39–45.

Feldstein AC, Elmer PJ, Nichols GA, Herson M (2005). Practice patterns in patients at risk for glucocorticoid-induced osteoporosis. *Osteoporos Int* **16:** 2168–2174.

Glowniak JV, Loriaux DL (1997). A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. *Surgery* **121:** 123–129.

Gonzalez-Moles MA, Scully C (2005). Vesiculo-erosive oral mucosal disease – management with topical corticosteroids: (2) Protocols, monitoring of effects and adverse reactions, and the future. *J Dent Res* **84:** 302–308.

Grinspoon SK (1994). Laboratory assessment of adrenal insufficiency. *J Clin Endocrinol Metab* **9:** 923–931.

Gulliver T, Eid N (2005). Effects of glucocorticoids on the hypothalamic–pituitary–adrenal axis in children and adults. *Immunol Allergy Clin North Am* **25:** 541–555.

Kehlet H (1975). A rational approach to dosage and preparation of parenteral glucocorticoid substitution therapy during surgical procedures. *Acta Anaesth Scand* **19:** 260–264.

Kehlet H, Binder C (1973). Value of an ACTH test in assessing hypothalamic–pituitary–adrenocortical function in glucocorticoid-treated patients. *Brit Med J* **2:** 147–149.

Key SJ, Hodder SC, Davies R, Thomas DW, Thompson S (2003). Perioperative corticosteroid supplementation and dento-alveolar surgery. *Dent Update* **30:** 316–320.

Komerik N, Akkaya A, Yildiz M, Buyukkaplan US, Kuru L (2005). Oral health in patients on inhaled corticosteroid treatment. *Oral Dis* **11:** 303–308.

Krasner AS (1999). Glucocorticoid-induced adrenal insufficiency. *JAMA* **282:** 671–676.

Liapi C, Chrousos GP (1992). Glucocorticoids. In: Yaffe SJ, Aranda JV, eds. *Pediatric pharmacology*, 2nd edn. WB Saunders: Philadelphia, PA, pp. 466–475.

Lipworth BJ (1999). Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* **159:** 941–955.

May ME, Carey RM (1985). Rapid adrenocorticotropic hormone test in practice. *Am J Med* **79:** 679–684.

Nieman LK (2003). Dynamic evaluation of adrenal hypofunction. *J Endocrinol Invest* **26** (Suppl. 7)**:** 74–82.

Salem M, Tainsh RE, Jr, Bromberg J, Loriaux DL, Chernow B (1994). Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. *Ann Surg* **219:** 416–425.

Salib RJ, Howarth PH (2003). Safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis. *Drug Saf* **26:** 863–893.

Sfzeler S, Rohatagi S, Williams J, Lloyd M, Kundu S, Banerji D (2005). Cicelsonide, a novel inhaled steroid, does not affect HPA axis function in patients with moderate to severe persistent asthma. *Chest* **128:** 1104–1114.

Speckart PF, Nicoloff JT, Bethune JE (1971). Screening for adrenocortical insufficiency with cosyntropin (synthetic ACTH). *Arch Intern Med* **128:** 761–763.

Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D (2002). Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* **87:** 457–461.

Walsh LJ, Wong CA, Oborne J *et al* (2001). Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax* **56:** 279–284.

Wogelius P, Poulsen S, Sorensen HT (2004). Use of asthma-drugs and risk of dental caries among 5 to 7 year old Danish children: a cohort study. *Community Dent Health* **21:** 207–211.