IN BRIEF

This paper :

- Reviews the physiology of glucocorticoids.
- Provides an update on the therapeutic applications of steroid drugs.
- Provides an understanding of the theoretical basis for adrenal crisis and collapse.
- Provides the dental practitioner with guidelines for management of patients being treated with steroid drugs.

Steroid cover for dental patients on long-term steroid medication: proposed clinical guidelines based upon a critical review of the literature

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Based to a great extent upon mainly anecdotal case reports and theory, there is a general acceptance that patients on long-term systemic steroid medication should receive supplementary glucocorticoids or 'steroid cover' when undergoing certain types of stressful treatment including dentistry. The theoretical basis to this practice is that exogenous steroids suppress adrenal function to an extent that insufficient levels of cortisol can be produced in response to stress, posing the risk of acute adrenal crisis with hypotension and collapse. The purpose of this paper is to review relevant literature and propose clinical guidelines for dental practitioners. Of numerous reported cases of adrenal crisis following procedural interventions, few stand up to critical evaluation. Other reviewers have reached similar conclusions. A number of studies confirm the low likelihood of significant adrenal insufficiency even following major surgical procedures. Various authors have suggested modified guidelines for management of patients on steroid medications. Patients on long-term steroid medication do not require supplementary 'steroid cover' for routine dentistry, including minor surgical procedures, under local anaesthesia. Patients undergoing general anaesthesia for surgical procedures may require supplementary steroids dependent upon the dose of steroid and duration of treatment.

INTRODUCTION

Glucocorticoids were first introduced in the 1940s and have become a widely prescribed class of drugs. Subsequently, concern developed regarding the potential of exogenous steroids to suppress normal adrenal gland function. This resulted in development of recommendations for additional glucocorticoid supplementation, or 'steroid cover', for management of patients undergoing stressful situations such as surgery or dentistry.[1–3] It has thus become common for standard textbooks in dentistry to recommend the administration of oral or intravenous steroids prior to even minor dental procedures such as conservative dentistry.[4] With the increased understanding of adrenal function and knowledge of glucocorticoids during the last 20 years, it is timely to review this knowledge with reference to whether accepted guidelines for steroid cover remain appropriate. A literature search was conducted through the National Library of Medicine PubMed database, using the search terms *adrenal crisis, adrenal collapse, adrenal suppression, Addisonian crisis, steroid cover,* covering literature up to December 2002. All identified publications were considered for the present review, excluding however those papers which did not add materially to the previously published body of knowledge on the subject.

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REVIEW OF LITERATURE

Physiology of glucocorticoids

The cortex of the adrenal gland produces both sex (androgens) and corticoid hormones, the latter being divided into mineralocorticoid (aldosterone) and glucocorticoid (cortisol) steroids. Glucocorticoids are principally concerned with glucose metabolism, have a 'permissive role' affecting many physiological processes, and also a limited mineralocorticoid effect altering electrolyte and fluid balance by increasing sodium and water retention.[5] Glucocorticoids play a critical role in the body's response to stress. Stress results in release of cytokines, and in particular the cytokine interleukin-1, which causes cortisol levels to rise thereby mobilising the body's glycogen and fat stores.[6]

Control of cortisol release is modulated through the hypothalamic-pituitary-adrenal (HPA) axis, whereby secretion of corti-

cotrophin-releasing hormone (CRH) from the hypothalamus in turn modulates release of adreno-corticotrophic hormone (ACTH) from the anterior pituitary gland. Cortisol release is in direct response to the action of ACTH. Cortisol, as well as exogenous glucocorticoids, functions to provide negative feedback on CRH release from the hypothalamus and thus ACTH.[5]

Glucocorticoid insufficiency

Thomas Addison, in 1855, described the clinical syndrome associated with disease of the adrenal glands. Primary Addison's disease follows destruction of the adrenal gland, resulting in decreased mineralocorticoid and glucocorticoid levels.[7] Autoimmune disease has now superseded tuberculosis as the most common cause of primary Addison's disease, while other causes are metastatic cancer, haemorrhage and fungal disease,[8] and an identical clinical state will also arise following adrenalectomy. Secondary Addison's disease results from deficiency of ACTH due to disease of the anterior pituitary gland, but may also result from the action of exogenous glucocorticoids in suppressing ACTH release. This leads to decreased glucocorticoid levels only, mineralocorticoid levels being not affected as they are controlled by the renin-angiotensin system.[7,9] Addison's disease may present either as a chronic illness, or as an Addisonian or adrenal crisis associated with a stressful event when cortisol levels fail to meet the body's increased requirements.

Adrenal or Addisonian crisis

Untreated adrenal failure is incompatible with life,[10,11] and acute adrenal insufficiency is primarily a state of mineralocorticoid deficiency.[12] However, patients taking exogenous steroids may sometimes develop coexistent autoimmune adrenal disease, and experience Addisonian crisis due to the mineralocorticoid deficiency alone.[12] Three clinical states associated with adrenal failure are considered to occur.

1. Acute adrenal crisis, with insufficiency of mineralocorticoids and glucocorticoids, is a medical emergency. The patient presents with abdominal pain, weakness, hypotension, dehydration, nausea and vomiting.[13] Laboratory findings may include decreased sodium (hyponatraemia), elevated potassium (hyperkalaemia), decreased blood glucose (hypoglycemia), acidosis and uraemia. Few patients have all these findings, with hypotension and nausea being most common.[14]
2. Patients with secondary Addison's disease present less acutely, because mineralocorticoid function is normal. The most typical presentation is of hypotension, and hyponatraemia without volume depletion.[9] Additional symptoms may include fatigue, weakness, arthralgia, nausea, and orthostatic dizziness associated with hypotension.
3. Patients taking exogenous glucocorticoids. Exogenous glucocorticoids can cause adrenal gland suppression and resultant atrophy. With atrophy of the adrenal glands there is a decreased glucocorticoid response to stress, and this may precipitate an adrenal crisis.[7]

Adrenal crisis and surgery

The stress of surgery may precipitate adrenal crisis in patients. Since 1952, fifty-seven cases have been reported of patients suffering fatal circulatory collapse following surgery, believed to be due to cortisol insufficiency, and these cases have been reviewed and summarised in the paper by Salem *et al.*[15] In reviewing these reports, firm evidence of definite adrenal insufficiency was however identified for only three cases, while in three further cases adrenal insufficiency was the likely cause. The remaining cases were inconclusive or not likely to have been related to cortisol levels. Cope[21] has stated that most reported cases of adrenal insufficiency 'were a failure of medical diagnostic skills not the adrenal glands.' It could thus reasonably be concluded that adrenal insufficiency leading to acute adrenal crisis is considerably over reported.

In oral and maxillofacial surgery two cases of adrenal crisis following dental extractions have been reported. In the case described by Cawson and James[16] a 49-year-old male, taking 5 mg prednisolone daily for rheumatoid arthritis, underwent general anesthesia for 15 dental extractions. The patient doubled his prednisolone dose on the day of the operation. Post-operatively he was referred to hospital with persistent bleeding and found to have blood pressure of 60 mm Hg systolic and 40 mm Hg diastolic. Blood pressure rose following administration of hydrocortisone, thus the hypotension was attributed to an adrenal crisis. In the case of Broutsas and Seldin[17] a 53-year-old woman, taking 37.5 mg cortisone (equivalent 7.5 mg prednisolone) for primary Addison's disease, had seven teeth extracted under general anesthesia. Additional doses of 100 mg cortisone were administered 12 and 6 hours preoperatively. Post-operatively she had low blood pressure and signs of shock that were attributed to adrenal crisis.

Both of these patients presented with low blood pressure post-operatively, which responded to the administration of hydrocortisone 100 mg at regular intervals over the following 2 days. However, the administration of intravenous hydrocortisone will produce a rise in blood pressure in healthy patients, and cannot thus be regarded in these two cases as *prima facie* evidence of acute adrenal insufficiency.[19] Hypotension following general anaesthesia can have numerous causes, including nausea and failure to restore volume following pre-operative fasting. Furthermore, neither cortisol levels nor electrolytes were assessed, and the patients were not worked up for other causes of hypotension. It is correspondingly inconclusive that adrenal crisis was the cause of hypotension in either case.

A further case of adrenal crisis was reported by Scheitler *et al.*,[18] involving a 43-year-old man undergoing tooth extraction under local anaesthesia. However this patient, who had well-documented secondary Addison's disease subsequent to pituitary surgery and radiotherapy, had a reaction involving high fever and raised blood pressure inconsistent with acute adrenal insufficiency. This case therefore does not meet any reasonable criteria for adrenal crisis.

Exogenous glucocorticoids and adrenal suppression

Every day, 24 to 30 mg of cortisol (equivalent to 5–7.5 mg prednisolone) is released in a rhythmic pulsatile fashion. Under stress this may increase to 300 mg (60 mg prednisolone equivalent) per day.[22] The existence of adrenal suppression can be tested by measuring the cortisol response to ACTH or insulin.[23]

Bromberg *et al.*[24] evaluated 60 transplant patients at the time of admission for surgery or for serious medical conditions. The patients had all been taking 5 to 10 mg prednisolone for longer than 3 months and had received no additional steroids. Compared with controls, the test group showed comparative cortisol levels in response to stress. However a study by Schlaghecke *et al.*,[25] of 279 patients receiving steroids, found a correlation between resting cortisol levels and dose of steroids, but little correlation between steroid dose and poor cortisol response to stress testing. Some patients on low doses of steroid did not mount an increased cortisol level after administration of insulin or ACTH. There is no explanation for why this last study conflicts with other published works, and generally it is accepted that adrenal suppression correlates with dose of glucocorticoids and length of treatment.[7,11]

It is well established that patients with documented suppression of adrenal function can undergo surgical treatment without event.[27] Glowniak and Loriaux[28] conducted a double blind study of 18 patients with proven HPA suppression undergoing

moderate to major surgery. The test group received supplementation of 200 mg cortisol for the first 24 hours followed by 100 mg the second day and 50 mg the third day, while the control group received only their regular steroid dose. Blood pressure peri-operatively was monitored, and no difference found between the two groups. One patient in each group developed post-operative hypotension but both responded to volume replacement. It may be that testing of cortisol response to ACTH or insulin is an unreliable surrogate end point for adrenal suppression, in other words the criteria measured are not a reflection or marker of the clinical situation.

In another study by Bromberg *et al.*,[29] 52 renal patients receiving between 10 and 15 mg prednisolone daily underwent moderate surgery without additional steroids. Monitoring of cortisol levels showed an increase in cortisol perioperatively and no patients had signs of adrenal crisis. Kehlet and Binder[30] studied 104 patients who ceased taking their regular dose of exogenous glucocorticoids 36 hours prior to surgery, and whose bloodpressure and cortisol levels were monitored throughout surgery. The majority of these patients maintained a normal adrenal cortical response.

Patients who exhibited lower resting cortisol levels than controls did not develop hypotension, when compared with patients with normal cortisol levels.

Seven patients experienced unexplained hypotension, four of whom had normal cortisol levels and three slightly decreased cortisol levels. The hypotension corrected spontaneously or following fluid replacement. It thus appears that HPA suppression does not correlate with the ability of the adrenal glands to respond to stress.

Dluhy,[31] in a review of inhaled steroids and glucocorticoid activity, concluded that inhaled steroids in high doses for a long term could lead to suppression of the HPA axis, possibly indicating the use of supplementary steroids during stress challenges. Recent case reports, well documented with respect to measuring cortisol levels and undertaking stress testing, have confirmed that high doses of inhaled steroids such as fluticasone and budesonide can cause adrenal suppression culminating in adrenal crisis.[32,33] Dluhy further concluded that the risk of adrenal insufficiency in patients taking low to medium doses of inhaled steroid was minimal, and did not indicate use of supplementary steroids.

Glucocorticoid dose and HPA suppression

Generally it is accepted that the degree of HPA suppression is related to the length of treatment and dose of steroids.[7,11,26] Long term steroid treatment, with doses equivalent to 10 mg prednisolone or greater, is mostly likely to cause HPA suppression.[26] This group of patients may develop symptoms of fatigue, weakness, arthralgia, nausea, and orthostatic dizziness if they abruptly stop steroids.[9] Salem[15] reviewed the literature on this topic, concluding that blanket recommendations for steroid cover were not supported by evidence and that more significance should be attached to the dose and duration of therapeutic steroid treatment. He additionally points out that patients taking doses above 50 mg prednisolone are close to the innate maximum cortisol level seen in patients when stressed, therefore maintenance of the usual steroid dose is more critical than supplementary steroid doses, a view supported by Glowniak.[28]

Daily doses of steroids at or below 5–7 mg prednisolone a day are considered by some authors to be under the physiological threshold for causing adrenal suppression. There is however no consensus as to whether HPA suppression can occur in patients taking low doses of steroids.[34]

In summary, adrenal suppression via the HPA axis is most likely to occur with high doses of steroids, however such suppression does not necessarily eliminate the normal cortisol stress response.

Recovery from HPA suppression

HPA recovery, following cessation of high dose short to medium term steroids, occurs within 2 months. Spiegel *et al.*[35] evaluated renal transplant patients who received 40–100 mg prednisolone daily for 2–4 weeks, demonstrating that all had recovered normal adrenal function by 7 days. Webb and Clark[36] evaluated cortisol levels in patients who received 40 mg prednisolone daily for 3 weeks and found cortisol levels normal after 4 days. Levic *et al.*[37] studied 10 multiple sclerosis patients administered 1000 mg methylprednisolone (equivalent to 1200 mg prednisolone) for 7 days, and found no HPA suppression 10 days after ending the therapy.

The natural history of recovery following prolonged suppression of the HPA axis is manifested as a depressed response to ACTH testing for 9 months or more.[38] However, as previously stated, this will not necessarily reflect the functional status of the HPA axis which in most instances will be normal.

Adrenocortical response to stress

Anxiety

Studies have evaluated what constitutes stress and causes increases in cortisol levels. Surprisingly, in both the study by Banks[39] of oral and maxillofacial surgery patients, and that of Udelsman *et al.*[41] of general surgery patients, it was demonstrated that apprehension about surgery is not a stimulus for adrenal cortical secretion.

Anaesthesia

No cases of adrenal insufficiency have been reported in patients undergoing procedures under local anaesthesia. In a study by Bunch *et al.*[51] of patients having third molar teeth removed under local anaesthesia, significant increases of cortisol levels did not occur. Similarly, in a small study Shepherd *et al.*[50] assessed cortisol levels in patients undergoing periodontal surgery under local anaesthesia alone or with conscious sedation. Cortisol levels fell during the 90 minutes procedure, a more significant fall occurring in the patients receiving conscious sedation.

Hempenstall *et al.*[52] compared cortisol levels in patients having either a general anaesthetic or sedation for surgical removal of third molar teeth. Cortisol levels remained unchanged in the sedation group but rose significantly after surgery in patients who had a general anaesthetic.

General anaesthesia alone will cause an increase in cortisol levels. Oyama *et al.* [46,47] measured cortisol levels in patients under general anaesthesia for 45 minutes prior to surgery, and found a steady increase in cortisol with a peak in the recovery phase. It has been shown by Crozier[49] that certain anaesthetic drugs may cause a fall in cortisol levels during the peri-operative phase, but rapid recovery to normal levels follows. Udelsman *et al.*[41] reported that reversal of general anaesthesia and extubation comprised a major stimulus to increase in cortisol levels, although levels were minimally altered during anaesthesia and surgery.

Surgery

Kehlet and Binder[30] measured cortisol levels in 74 patients previously treated with glucocorticoids, who underwent major surgery without steroid supplementation. Eighteen patients developed post-operative hypotension, but in all cases the hypotension corrected spontaneously. Three of these patients were considered to have mild adrenocortical deficiency based on measured cortisol levels. These authors concluded that cortisol levels were not the primary determinant of hypotension in glucocorticoid-treated patients, and that acute stress-induced adrenocortical deficiency in such patients was likely to be infrequent. Naito *et al.*[45] studied the changes in plasma cortisol levels during and following major abdominal surgery, demonstrating the expected elevations and defining the mechanisms involved. Complete normalisation of cortisol levels after major surgery may take up to 72 hours, with significant elevation occurring only in the first 48 hours. King *et al.*[48] measured cortisol levels

in patients undergoing laminectomy, with comparable findings of a modest increase immediately following surgery. Crozier *et al.*[49] studied patients undergoing minor orthopedic procedures, with similar findings, cortisol levels returning to normal by 6 hours. Chernow *et al.*[53] demonstrated a direct correlation between the degree of surgical stress and elevation of plasma cortisol, with minor procedures having a negligible effect compared with major surgery, with return to normal levels usually within 24 hours.

Dentistry

There is a relative paucity of studies examining whether routine dental treatment has an effect on plasma cortisol levels. However some studies have examined salivary cortisol levels as these are considered by some authors to correlate well with plasma cortisol levels,[54] although other studies[55] have suggested a better correlation of urinary cortisol levels with those of plasma. Investigations by Brand,[55] Miller *et al.*[56] and Akyuz *et al.*[57] have shown an increase in salivary cortisol levels both before and during restorative dental treatment. Additionally, the study by Brand demonstrated persistent elevated urinary levels of cortisol following treatment.

Banks[39] studied 50 healthy patients undergoing general anaesthesia for third molar surgery, mandibular osteotomies or dental clearances. In these patients cortisol levels rose approximately 4 hours after surgery and returned to base line levels by 24 hours. On the basis of these findings Banks concluded that routine oral and maxillofacial surgery constituted minor surgery and would not warrant more than 1 day of steroid supplementation.

A more recent study by Thomason *et al.*[40] examined the need for supplementary steroids in organ transplant patients undergoing gingival surgery. This well-designed study identified no differences between one group receiving supplementary hydrocortisone 100 mg and another receiving placebo, when assessed by measurement of blood pressure and ACTH levels.

PROPOSED CLINICAL GUIDELINES

Glucocorticoid supplementation or 'steroid cover'

General dental procedures for patients receiving long-term steroid medication do not warrant supplementation with additional glucocorticoids.

Patients undergoing minor surgical procedures under local anaesthesia are at very low risk, if any, for developing adrenal crisis. Although opinions conflict on whether any significant suppression of adrenal function occurs in patients taking low doses of steroids (under 7.5 mg prednisolone) available evidence suggests that supplementation is unnecessary for local anaesthetic procedures. These patients should simply maintain their usual dose of glucocorticoids. However those patients taking high doses of steroid should double the usual dose on the day. Unexplained hypotension in patients on exogenous steroids should be investigated for other possible causes, because adrenal crisis is rare and patients on glucocorticoids are at high risk of various other medical complications. If adrenal insufficiency is suspected, follow-up with an endocrinologist is important, as secondary adrenal disease needs to be ruled out.

For surgical procedures under general anaesthesia, the need for peri-operative glucocorticoid supplementation, for patients on exogenous steroids, should be determined by the severity of the surgery and the pre-existing glucocorticoid dose, and there is no evidence that glucocorticoid supplementation exceeding physiological levels of cortisol induced by stress is beneficial. Thus, for patients undergoing general anesthesia for minor surgery 100 mg hydrocortisone intramuscularly should be administered and the usual glucocorticoid medications maintained. For major surgery 100 mg hydrocortisone delivered as a bolus pre-operatively followed by 50 mg 8-hourly for 48 hours is adequate.

An alternative regimen for surgical patients is that proposed and successfully trialled by Lloyd[42] for orthopaedic patients, where hydrocortisone was given as required based on measurement of post-operative levels of blood pressure and pulse rate. It was found that 78% of patients required no supplementation, and surprisingly small doses for those who did. A further option is to undertake pre-operative stress testing by assessing cortisol response to insulin or ACTH challenge.

The risks of excess glucocorticoid administration are relatively small, involving mainly impaired electrolyte balance and hypertension,[10] however pharmacotherapy should be based on current scientific and clinical knowledge, thus decreasing overtreatment and inconvenience to patient and practitioner.

SUMMARY

Patients with primary Addison's disease are most at risk of acute adrenal insufficiency. The risk of clinically significant adrenal insufficiency is low in patients taking long-term steroid medication. For this latter group of patients, performance of routine dentistry including minor surgical procedures under local anaesthesia does not require supplementary steroids. For patients undergoing surgery under general anaesthesia, provision of supplemental glucocorticoids needs to be balanced against the dose and duration of treatment with steroid drugs and the severity of the planned surgery.

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