Management of adrenal insufficiency during the stress of medical illness and surgery

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ABSTRACT

- Patients with adrenal insufficiency (AI) require additional glucocorticoid doses during surgery or medical illness, but there is no universally accepted regimen for glucocorticoid supplementation therapy.
- The high doses and long duration of glucocorticoid coverage that have traditionally been used do not reflect the hypothalamic–pituitary–adrenal response to surgical stress and medical illness in normal people.
- While the optimal dose and duration of supplementation therapy have not been established, our recommendations are based on extrapolation from what constitutes a normal cortisol response to stress, on expert opinion derived from the medical literature, and on clinical experience.
- The recommended use of lower doses of glucocorticoids during surgical and medical stress should not de-emphasise the importance of additional supplementation during such events.
- Our recommendations do not replace clinical judgement, but their use will ensure that patients with AI are safely managed during illness or surgery without the risk of an adrenal crisis or excessive steroid dosing.

MJA 2008; 188: 409–413

It has been known since the mid 19th century that the adrenal cortex is essential for life.[1] However, life-saving glucocorticoid replacement therapy for adrenal insufficiency (AI) was not widely available until the clinical introduction of cortisone in 1949.[2] The initial standard of care established for glucocorticoid supplementation therapy during stress in hypoadrenal patients was based on early case reports of adrenal crises in patients not receiving adequate perioperative glucocorticoid coverage.[3,4] Over the past decade, there has been a shift in clinical practice in favour of giving lower doses and shorter duration of glucocorticoids, according to the severity and duration of illness or surgery.[5-7] The recommendations for glucocorticoid supplementation presented here will provide useful information for physicians, anaesthetists, surgeons, dentists, obstetricians and general practitioners. We will not address the controversial issue of relative AI in the setting of critical illness.[6,8]

Normal cortisol production

Glucocorticoids are produced in the zona fasciculata of the adrenal cortex under the regulation of the hypothalamic–pituitary–adrenal (HPA) axis (Box 1).[7] Corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which are synthesised in the hypothalamus, stimulate the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, which in turn results in the production of cortisol, the main endogenous glucocorticoid.[7,8] Cortisol exerts negative feedback at the level of both the hypothalamus and the pituitary gland.[7] Cortisol circulates in the plasma both in the free form (about 5%) and protein-bound (predominantly to corticosteroid-binding globulin [CBG]). Further regulation of glucocorticoids occurs at a cellular level by the action of the 11-β-hydroxysteroid dehydrogenase enzymes and expression of the glucocorticoid receptor.

Earlier estimates of endogenous cortisol production were 12 mg/m^2/day.[9] However, using newer analytical methods, Esteban et al[10] and Kerrigan et al[11] showed that the cortisol production rate in normal subjects was significantly lower than previously believed. Both studies found that the mean cortisol production rate was 5.7 mg/m^2/day, or about 10 mg/day.[10,11]

Cortisol response to stress

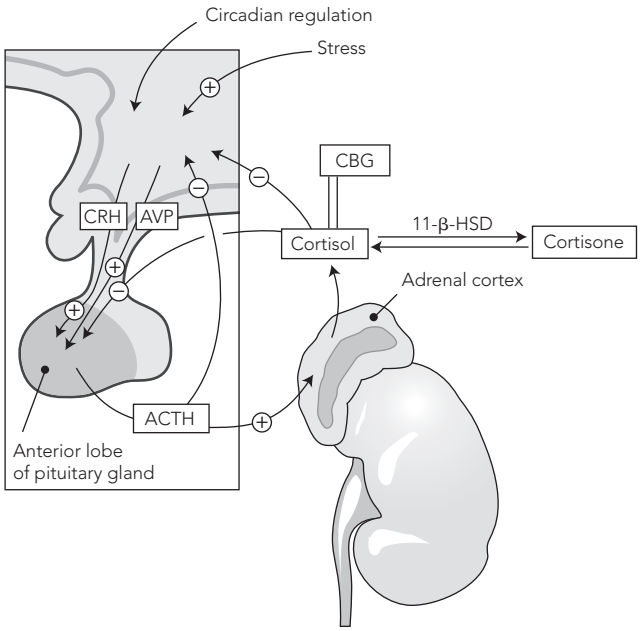
Cortisol has many important metabolic and endocrine functions that are essential for human survival, particularly during stress. Surgery, anaesthesia, trauma, and severe illnesses result in elevated plasma ACTH and cortisol levels.[7,8] Cortisol is required for the metabolism of carbohydrates, lipids and proteins, and for the maintenance of vascular tone and endothelial integrity.[7,8] It also potentiates the vasoconstrictor actions of catecholamines[12] and has anti-inflammatory effects on the immune system.[7,8] Aldosterone, synthesised in the adrenal zona glomerulosa under the control of the renin–angiotensin system, regulates sodium and potassium balance and intravascular volume.[7]

Surgery is one of the most potent activators of the HPA axis.[13] Recent studies have reported on HPA axis function during and after various surgical procedures, including cholecystectomy,[14] pancreatoduodenectomy,[15] coronary artery bypass graft (CABG) surgery,[16] pituitary adenomectomy[17] and neck exploration.[18] The maximum ACTH and cortisol levels are reached in the early postoperative period, especially following anaesthesia reversal and endotracheal extubation.[14,16,18] In patients undergoing CABG surgery, plasma cortisol levels increase significantly during the operation, with peak cortisol levels achieved 30 minutes after extubation (median, 744 nmol/L; interquartile range, 645–1062 nmol/L).[16] While ACTH levels return to the normal range within 24 hours,[8,15-18] cortisol levels decline more slowly, reaching high normal values about 48–72 hours after surgical procedures.[8,17,18] From a normal secretion rate of 10 mg/day,[10,11] cortisol production rate increases to 75–150 mg/day after major surgery.[19]

Adrenal insufficiency

The most common cause of primary AI (Addison's disease) in developed countries is autoimmune adrenalitis, which can arise in isolation or as part of an autoimmune polyglandular syndrome.[20,21] Other causes of primary AI include infections (tuberculosis, cryptococcosis), genetic disorders (adrenoleukodystrophy, adrenomyeloneuropathy), bilateral adrenal haemorrhage, metastases and surgery.[20,21] In primary AI, all layers of the adrenal cortex

1 Regulation of the hypothalamic–pituitary–adrenal axis*



ACTH = adrenocorticotropic hormone. AVP = arginine vasopressin. 11-β-HSD = 11-β-hydroxysteroid dehydrogenase. CBG = corticosteroid-binding globulin. CRH = corticotropin-releasing hormone.

* Cortisol circulating in the plasma is predominantly protein-bound (to CBG). Cortisol and the inactive glucocorticoid cortisone are interconverted by the 11-β-HSD enzymes. ◆

2 Glucocorticoid preparations

Steroid	Biological half-life (hours)	Relative glucocorticoid potency	Approximate bioequivalent dose (mg)*
Hydrocortisone	8–12	1	20
Cortisone acetate	8–12	0.8	25
Prednisolone, prednisone	18–36	4	5
Dexamethasone	36–54	25–50	0.5

* Approximate bioequivalent dose indicates the doses of the different steroids at which a similar glucocorticoid effect is achieved. The doses listed above are close to the physiological daily maintenance requirement for an average person.[22,29] ◆

are affected, resulting in glucocorticoid, mineralocorticoid and adrenal androgen deficiencies.[20,21]

Secondary AI arises from pituitary or hypothalamic dysfunction or failure caused by tumours, irradiation, infiltration, trauma or surgery.[20,21] Deficiency of ACTH or CRH leads to atrophy of the adrenal zona fasciculata, resulting in glucocorticoid insufficiency. Mineralocorticoid deficiency does not occur in secondary AI because the renin–angiotensin–aldosterone system remains intact.

Iatrogenic AI is caused by suppression of the HPA axis due to glucocorticoid therapy in pharmacological doses.[22] Traditionally, it was believed that the degree of HPA suppression and adrenal atrophy in patients receiving exogenous glucocorticoids was related to the duration and dose of therapy.[22,23] In patients taking any steroid dose for less than 3 weeks, suppression of the HPA axis is rarely clinically significant.[23] Conversely, any patient who has received the equivalent of 15 mg/day of prednisolone for more than 3 weeks should be suspected of having HPA suppression.[23] However, recent studies have found poor correlation between HPA axis function and the cumulative dose, the highest dose or the duration of therapy.[24,25] Because of the considerable inter-individual variability in the degree and duration of adrenal suppression, it is difficult to accurately predict which patients will develop AI when glucocorticoid treatment is discontinued.[6]

Some medications other than glucocorticoids may suppress HPA function and place patients at risk of developing AI. Progestational agents such as medroxyprogesterone and megestrol have glucocorticoid activity.[8] Enzyme inducers such as rifampicin and carbamazepine enhance the clearance of some synthetic glucocorticoids. Inhibitors of cortisol synthesis include ketoconazole, aminoglutethimide, and etomidate (an anaesthetic agent that selectively inhibits adrenal 11-β-hydroxylase, the enzyme that converts 11-deoxycortisol to cortisol).[26]

Management of adrenal insufficiency

Glucocorticoid replacement therapy in AI is usually lifelong for patients with adrenal, pituitary or hypothalamic disorders. In patients with iatrogenic AI, glucocorticoid replacement is required until recovery of the HPA axis. Issues regarding the optimal dose, timing of administration and choice of glucocorticoid, as well as methods for assessing replacement therapy, continue to be debated in the literature.[20,27]

The traditional replacement dosage of hydrocortisone has been 20–30 mg per day, taken orally in divided doses.[7] However, based on recent studies of daily cortisol production rates,[10,11] some authors have recommended a lower dose of 15 mg daily.[27] Optimal hydrocortisone replacement involves dosing two to three times daily,[27,28] while longer-acting synthetic glucocorticoids such as prednisolone can be given once daily. The biological half-life and relative potency of commonly used glucocorticoid preparations are outlined in Box 2. Although some experts favour hydrocortisone for replacement therapy in AI,[20] there are no outcome data to support the use of one glucocorticoid over another.[27] Whatever glucocorticoid is chosen, the clinician must be alert to the clinical features of excessive or inadequate replacement, as no clear optimal method of biochemical monitoring has been established.[27] In patients treated with hydrocortisone, use of the cortisol day curve, based on serum samples,[28] saliva or blood spots from capillary finger-prick samples,[30] has been advocated. Further work is needed to clarify whether such monitoring improves outcomes in patients receiving routine replacement doses.

Patients with primary AI also require mineralocorticoid replacement with fludrocortisone 0.05–0.2 mg daily. The dose is adjusted based on serum sodium and potassium levels, blood pressure and plasma renin activity.[7,20,21] Fludrocortisone is not required for treatment of secondary AI. The issue of adrenal androgen replacement with dehydroepiandrosterone[20] will not be addressed here.

Glucocorticoid supplementation therapy during stress and illness

Soon after the introduction of glucocorticoid therapy for rheumatic diseases in 1949,[2] case reports appeared describing perioperative hypotensive crisis and mortality related to presumed

iatrogenic AI. In 1952, Fraser et al described a patient with rheumatoid arthritis who developed circulatory shock as a consequence of preoperative withdrawal from glucocorticoid therapy.[3] A year later, a similar case report concluded with a list of recommendations for perioperative glucocorticoid coverage (intramuscular cortisone 100 mg daily plus ACTH injections).[4]

Since then, a number of different schedules for glucocorticoid supplementation therapy have been proposed. These can be broadly divided into two groups. Some have been founded on an empirical basis, often using high-dose glucocorticoid therapy (eg, hydrocortisone 200 mg daily or more for major surgery),[13,23,31] while others have been based on the estimated cortisol production rate for different levels of stress.[5-7,19,32] Kehlet[19] concluded that, based on the available data,[33-36] a reasonable estimate of cortisol secretion during the 24 hours after major surgery was 75–150 mg. For major surgery, a hydrocortisone dose of 100 mg/day was recommended; for minor surgery, the recommendation was to give 25 mg hydrocortisone with induction of anaesthesia and the usual glucocorticoid dose postoperatively.

Twenty years later, Salem et al[5] reviewed the data on cortisol secretion during surgery and after stimulation with exogenous ACTH, and published recommendations for perioperative glucocorticoid coverage during minor, moderate and major surgical procedures. Inder and Hunt[32] proposed a reducing schedule for patients with secondary AI undergoing pituitary surgery: this involved intravenous hydrocortisone 50 mg given 8-hourly on the day of surgery, 25 mg given 8-hourly on the first postoperative day, and a return to maintenance doses by Days 2–3. Subsequent reviews[6,7] have also concurred with the rationale for glucocorticoid supplementation that reflects the complexity and duration of the procedures.

In patients with AI who are fasting before procedures, glucocorticoid therapy must be continued, by parenteral routes if necessary. A recent case report has highlighted the adverse consequences of omitting oral steroid therapy in a patient who was fasting before a surgical procedure. The patient developed hypotension and acute renal failure.[37] Although it is well known that patients with AI require perioperative glucocorticoid supplementation therapy,

3 Guidelines for glucocorticoid supplementation in patients with adrenal insufficiency

Surgical stress	Glucocorticoid dosage*	Medical stress	Glucocorticoid dosage
Minimal		Minimal	
< 1 hour under local anaesthesia (eg, for routine dental work, skin biopsy)	Usual replacement dose, 15–30 mg hydrocortisone/day	Non-febrile cough or upper respiratory tract infection	Usual replacement dose, 15–30 mg hydrocortisone/day
Minor		Minor	
Inguinal hernia repair Colonoscopy	Intravenous hydrocortisone 25 mg or equivalent at start of procedure. Usual replacement dose after procedure	Viral illness Bronchitis Uncomplicated urinary tract infection Uncomplicated cellulitis	Double or triple the usual daily dose of glucocorticoid until recovery (eg, oral hydrocortisone 40–60 mg/day in divided doses)
Dental procedures requiring > 1 hour under local anaesthesia (eg, multiple extractions, periodontal surgery)	Double the daily dose of glucocorticoid on day of procedure (eg, 40 mg oral hydrocortisone). Usual replacement dose next day		
Moderate		Moderate	
Open cholecystectomy Segmental colon resection Lower limb revascularisation Total joint replacement Abdominal hysterectomy	Intravenous hydrocortisone 75 mg/day on day of procedure (eg, 25 mg 8-hourly). Taper over next 1–2 days to usual replacement dose in uncomplicated cases	Gastroenteritis Pneumonia Pyelonephritis	Intravenous hydrocortisone 25 mg 8-hourly until recovery
Severe		Severe	
Cardiothoracic surgery Whipple's procedure Oesophagogastrectomy Total proctocolectomy Liver resection Pituitary adenomectomy Dental procedures under general anaesthesia, orthognathic surgery, severe facial trauma	Intravenous hydrocortisone 150 mg/day (eg, 50 mg 8-hourly). Taper over next 2–3 days to usual replacement dose in uncomplicated cases	Pancreatitis Myocardial infarction Labour	Intravenous hydrocortisone 150 mg/day (eg, 50 mg 8-hourly). Taper once clinical condition stabilises
Critical illness/intensive care		Critical illness/intensive care	
Major trauma Life-threatening complication	Maximum 200 mg/day intravenous hydrocortisone (eg, 50 mg 6-hourly, or by continuous infusion)	Septic shock	Maximum 200 mg/day intravenous hydrocortisone (eg, 50 mg 6-hourly, or by continuous infusion)

*Give parenterally if fasting. Guidelines based on extrapolation from various sources.[5-8,20-22,27,29,32,38] ◆

serious omissions can occur as a result of inadequate or unclear instructions from the treating team.[37] Therefore, it is important to clearly document and institute an appropriate perioperative glucocorticoid management plan.

The findings of studies examining the normal cortisol response to surgery[8,17,18] support the concept that increased glucocorticoid coverage is not required in patients with AI beyond 3 days in uncomplicated surgical cases. Potential side effects of prolonged or excessive steroid use include hyperglycaemia, impaired wound healing and an increased susceptibility to infection caused by immune suppression.[5,8]

Recommendations regarding glucocorticoid coverage during non-surgical illnesses are largely based on expert consensus. Patients have traditionally been advised to double or triple their daily dose of glucocorticoid therapy during a febrile illness until recovery.[20,21,27,38] Glucocorticoids should be administered parenterally, preferably intravenously, in cases of vomiting or diarrhoea.[20] For patients who have a critical illness such as septic shock, Coursin and Wood[7] have recommended 50–100 mg of hydrocortisone every 6–8 hours or 0.18 mg/kg/hr as a continuous intravenous infusion, together with fludrocortisone 0.05 mg daily. The current evidence does not support the use of hydrocortisone doses above 200 mg/day.[8] Arafah reported that after intravenous boluses of hydrocortisone 50 mg had been given 6-hourly, peak plasma cortisol levels were over 100 μg/dL (2760 nmol/L), and nadir levels remained elevated at 40–50 μg/dL (1100–1380 nmol/L).[8] Keh et al[39] showed that, during continuous hydrocortisone infusion (10 mg/hr), plasma total cortisol levels were over 3000 nmol/L — well above the levels reported in patients with septic shock (mean, 880 nmol/L; SEM, 79 nmol/L).[40] Another study found that the majority of cortisol levels were between 552 and 1242 nmol/L in intensive care unit patients with severe sepsis or septic shock.[41] While it is evident that the glucocorticoid dose should not exceed 200 mg/day,[8] the *optimal* dose for managing septic shock in patients with AI has not been evaluated in controlled clinical trials. Mineralocorticoid supplementation with fludrocortisone is not required in patients with secondary AI or in those with primary AI receiving more than 50 mg hydrocortisone daily, given its potent mineralocorticoid activity at high doses.[8]

Recommendations for glucocorticoid supplementation therapy during surgery or medical illness are outlined in Box 3. These recommendations are based on extrapolation from what constitutes a normal cortisol response to stress[5,19,33-36] and on expert opinion.[5-8,20,21,27,32,38] After the administration of intermittent exogenous glucocorticoids, transient increases in plasma cortisol occur that exceed the binding capacity of CBG,[42] leading to the rapid clearance of cortisol. Therefore, it may be argued that comparing the total dose of exogenous glucocorticoid required with the endogenous cortisol secretion rate during stress is not valid. However, based on clinical experience and review of the literature, it is safe to treat patients with doses similar to those that mirror the normal physiological response to stress. The recommendations given in Box 3 address the need for increased glucocorticoid supplementation in patients with AI during medical and surgical stress without exposing patients to excessive or prolonged steroid dosing.

During the course of a major illness or surgery, situations may arise in which patients do not appear to "respond" to the recommended glucocorticoid supplementation therapy. It is important to identify and treat other causes of clinical deterioration, such as sepsis or hypovolaemia.[6] If there is evidence of a new stressor or a complication, the continued glucocorticoid supplementation should be consistent with the stress response.[5]

For patients treated with glucocorticoid therapy who are suspected of having iatrogenic AI, some authors have advocated the use of the short ACTH 1-24 (Synacthen) test preoperatively to determine the actual need for increased glucocorticoid supplementation,[5] while others have followed the practice of empirical universal coverage given to all patients.[22] Providing universal coverage is more feasible than performing preoperative stimulation tests on all such patients.[22] Patients receiving topical (inhalation, intranasal or transdermal) glucocorticoids have a low risk of HPA suppression, and some authors have advocated no additional steroid coverage for these patients during minor to moderate illnesses, provided that their clinical course is uncomplicated.[6] However, adrenal suppression due to topical glucocorticoids has been described,[43] and a case can be made for providing steroid coverage for any patient who has received glucocorticoid therapy for more than 3 weeks by any route. Supplementing these patients, who may be at risk of HPA suppression, eliminates the risk of adrenal crisis. Furthermore, short courses (<48 hours) of increased glucocorticoid therapy rarely cause significant complications.[22]

Previous studies have shown that cortisol and ACTH levels increase during normal pregnancy, particularly in the second and third trimesters.[44] Some authorities have recommended increasing glucocorticoid replacement doses by 50% in the last trimester of pregnancy for women with AI.[20] Whether this is advisable may depend on the patient's usual treatment dose, as it has been shown that a dose increase is rarely necessary in women treated with 20–30 mg hydrocortisone daily.[27,45] Steroid management during labour[20,27] is outlined in Box 3.

Conclusions

Patients with AI require additional glucocorticoid doses during severe illness or surgery, but the optimal dose, frequency and duration of supplemental therapy remain contentious. Advances in our knowledge of the HPA axis function during stress have prompted reassessment of earlier recommendations for glucocorticoid coverage.[5-7] There is no evidence to support excessive dosing (> 200 mg hydrocortisone equivalent/day) or extensive duration of glucocorticoid therapy in uncomplicated cases.[8] While these recommendations do not replace clinical judgement, using them will ensure that patients with adrenal insufficiency safely navigate illness episodes or surgical procedures without excessive steroid dosing.

Competing interests

None identified.

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(Received 29 Jul 2007, accepted 5 Nov 2007) ❑