



Perioperative management of patients treated with glucocorticoids

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The introduction of cortisone therapy for anti-inflammatory and immunosuppressive purposes in 1948 was a major advance in medical therapeutics [1–3]. Within a few years, synthetic analogs of cortisone were also available and widely used. The introduction of glucocorticoids, however, created diseases of medical progress (ie, secondary adrenal insufficiency and exogenous Cushing's syndrome). This article addresses adrenal suppression and secondary adrenal insufficiency caused by glucocorticoid administration and the implications for the management of the surgical patient. Adrenal suppression, that is, abnormal adrenal function as a result of glucocorticoid therapy, occurs without hypotension. Secondary adrenal insufficiency caused by glucocorticoid therapy is a clinical entity in which hypotension occurs because of an adrenocorticotropic hormone (ACTH) deficiency induced by glucocorticoid administration. Adrenal suppression is much more common than adrenal insufficiency and is of concern because of the possibility that overt adrenal insufficiency may occur, especially under stressful conditions such as general anesthesia and surgery. Whereas ACTH administration causes Cushing's syndrome, secondary adrenal insufficiency does not accompany the use of ACTH for therapeutic purposes. For other reasons, ACTH is indicated only for diagnostic but not for therapeutic purposes [4,5].

Secondary adrenal insufficiency caused by glucocorticoid therapy was first identified a half century ago. Since that time our understanding of the natural history of hypothalamic–pituitary–adrenal (HPA) suppression resulting from glucocorticoid therapy and our approaches to management have been refined. The magnitude of the problem is great. In 2001, 34,124,000 prescriptions were written in the United States for the four most commonly used oral glucocorticoids (prednisone, methylprednisolone, prednisolone and

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dexamethasone) [6]. Also, patients may develop adrenal insufficiency from topical glucocorticoids, inhaled glucocorticoids and regional administration of glucocorticoids to other parts of the body. The risk factors for development of adrenal suppression from topical steroids for dermatologic indications include:

- Application to a large surface area of skin
- Application for a prolonged period of time
- Use of occlusive dressings
- Use of highly potent (class I) glucocorticoid agents

Similarly, the development of adrenal suppression from inhaled steroids is related to dose, duration of therapy and use of a potent agent (specifically fluticasone) [7].

This article addresses adrenal suppression and secondary adrenal insufficiency in patients treated with glucocorticoids. It does not address other aspects of glucocorticoid therapy or the use of glucocorticoids in critically ill patients. Reviews of these subjects may be found elsewhere [4,5,8].

Recognition of adrenal insufficiency caused by glucocorticoid therapy

Within a few years of the introduction of cortisone and ACTH into clinical practice, patients were identified in whom shock was attributed to adrenocortical insufficiency induced by these agents [4,9]. Although reports were published in which intraoperative or postoperative shock was attributed to previous treatment with ACTH, in no case then or subsequently was this diagnosis confirmed by the measurement of a plasma cortisol level or by a comparable test [4]. The development of secondary adrenal insufficiency caused by glucocorticoid therapy was confirmed as a real entity and remains a problem.

In the early reports, shock developed after a course of therapy lasting from 2 weeks to several years. At the time, biochemical tests of adrenocortical function had not been developed. The diagnosis was usually based on the development of hypotension without other apparent cause and apparent response to glucocorticoid therapy [4]. In other cases, the diagnosis was based on the presence of adrenal atrophy at autopsy [4]. It subsequently became apparent that making the diagnosis of acute adrenal insufficiency without laboratory evidence is not reliable [10,11]. As long ago as 1966, Cuthbert L. Cope noted that “the vast majority of such incidents seem to be associated with medical diagnostic, and not adrenal, failure” [12]. In most instances in which hypotension is attributed to the effects of glucocorticoid therapy, hypotension is caused by problems such as volume depletion, sepsis, myocardial infarction or the effects of anesthetic and other medications. (Rarely, hypotension is caused by primary adrenal insufficiency or secondary adrenal insufficiency resulting from hypothalamic or pituitary disease.) In 1961 a case of adrenal insufficiency attributed to glucocorticoid therapy was at last

confirmed by the finding of low plasma cortisol levels [13]. Only a few such cases have been reported [13–15].

Prolonged hypotension and a response to adequate doses of a glucocorticoid agent are not reliable ways to assess adrenocortical function. One must also demonstrate plasma cortisol levels that are inappropriate (ie, below the values found in normal subjects under comparable stress).

Pathogenesis of hypotension in patients previously treated with glucocorticoids

Glucocorticoids have a permissive effect on vascular tone and blood pressure [16]. That is, they enhance vascular responsiveness to vasopressors (eg, catecholamines) without necessarily having an effect when given alone. This effect occurs at the level of the local vasculature and does not require central or systemic mediation [16]. The effect of glucocorticoids on vascular tone may be mediated by inhibition of prostacyclin (PGI₂) production by vascular endothelium and perhaps other cells [16–18]. Loss of the inhibitory effect of glucocorticoids on vascular tone during glucocorticoid deficiency may cause enhanced PGI₂ production, vasodilatation, and hypotension. Other mechanisms for the permissive effect of glucocorticoids on vascular tone may contribute [16].

The hypotension of secondary adrenal insufficiency in patients treated with glucocorticoids is not caused by mineralocorticoid deficiency. The secretion of aldosterone, the principal mineralocorticoid in humans, is regulated primarily by the renin-angiotensin system, which remains intact during glucocorticoid therapy. Whereas ACTH also stimulates aldosterone secretion, this effect is small compared with the effect of angiotensin II. ACTH deficiency does not result in aldosterone deficiency.

Incidence of perioperative adrenal insufficiency in patients treated with glucocorticoids

Perioperative adrenal insufficiency of any etiology is uncommon [9]. The incidence has been reported to be 0.01% (1 patient in 6947 urologic surgical procedures) [19] and 0.1% (five patients in 4364 cardiac surgical procedures) [20]. Among 62,473 anesthetic administrations, glucocorticoid coverage was required in 419 patients (0.7%) but only 3 episodes (0.7%) of hypotension attributable to inadequate glucocorticoid coverage were observed [21].

The incidence of perioperative adrenal insufficiency in patients treated with glucocorticoids is difficult to determine but must be low. As already noted, the early case reports were inconclusive and lacked biochemical confirmation of adrenal insufficiency [4,9,22]. In fact, there are so few reported cases with biochemical confirmation that one might question the

existence or importance of this entity. Nevertheless, well-documented cases have been reported [9,13–15]. Cases are encountered in clinical practice, but are infrequent. The paucity of reported cases probably reflects to some degree the low incidence of this problem. Awareness of the nature of the problem and its preventability has presumably reduced the actual frequency of the problem. It is probably also underreported for the following reasons:

- Such reports are not likely to appeal to potential authors and editors because previous publications have established the principle; and
- Reporting new cases might also be unappealing because such cases would represent failure to meet the standard of care that now exists.

Thus, perioperative hypotension and death are real hazards in patients treated with glucocorticoids but are uncommon. Not surprisingly, recent attention in the care of glucocorticoid-treated patients has been directed at more common complications, such as opportunistic infections and osteoporosis [5]. Nevertheless, the physician must have an approach to the prevention, identification, and treatment of an uncommon but potentially lethal event in patients exposed to glucocorticoid therapy.

The few well-documented published cases of steroid-induced adrenal insufficiency do not provide sufficient information to guide clinical practice with respect to diagnosis of HPA suppression and the risk for overt adrenal insufficiency. They do not reveal how long it takes for adrenal suppression to develop in steroid-treated patients, the doses that cause adrenal suppression, or how rapidly HPA function recovers following cessation of glucocorticoid therapy. Thus, investigators have sought to develop alternate or surrogate means to determine the answers to these important questions. The results of their labors are addressed later in this article.

Pitfalls in the study of adrenal insufficiency in patients treated with glucocorticoids

Because many patients are exposed to glucocorticoid therapy but few develop clinical manifestations of adrenal insufficiency, any test must be sensitive, specific and inexpensive.

The published literature on this subject is plagued by several recurrent problems of study design and interpretation. These include:

- Variations from study to study in the tests used to measure adrenal insufficiency and how they are applied (eg, the interval between cessation of steroids and performance of adrenal function tests) [4,23].
- Use of surrogate markers of adrenal function (such as an ACTH stimulation test) without correlation of these results with the response to clinically important stresses such as general anesthesia and surgery [24].
- The notorious difficulty of estimating the previous doses, cumulative doses and duration of glucocorticoid therapy [4,9].

- The assumption that partial suppression of the adrenocortical response to a provocative test indicates sufficient dysfunction to cause overt adrenal insufficiency.

The last point warrants further consideration. Partial suppression of the adrenocortical response to ACTH or another provocative test does not establish that a patient is unable to tolerate general anesthesia and surgery. Some glucocorticoid treated patients have tolerated general anesthesia and surgery without perioperative glucocorticoid coverage, including some who had subnormal plasma cortisol responses to ACTH or insulin-induced hypoglycemia [9,20,25–27]. The explanation for this variability is not clear. One possibility is that the system has redundancy or reserve function, so that a reduced level of function is not associated with clinical sequelae. This is true in many biologic systems. The permissive effect of glucocorticoids on vascular tone requires modest doses, in the range of basal physiologic (or replacement) doses. Consequently, normal basal levels may be sufficient to maintain vascular tone and failure to respond to a provocative test may not predict adrenal insufficiency during general anesthesia and surgery. In some instances, however, a reduced response to a provocative test is associated with inability to tolerate general anesthesia and surgery. Additional considerations may be variability from patient to patient in the circulating level of cortisol required to maintain vascular tone and differences in the degree of stress to which a patient is exposed.

A state of cortisol resistance (analogous to insulin resistance) may occur during stress in critically ill patients [8,28]. Cytokines such as interleukin (IL)-1, IL-6, interferon α , and the combined effects of IL-2 and IL-4 can cause glucocorticoid resistance, due at least in part to a reduction in glucocorticoid receptor-binding affinity [8,28]. This may be related to interactions of cytokine-stimulated transcription factors activator protein-1 (AP-1) and nuclear factor kappa B (NF- κ B) with the glucocorticoid receptor. Thus, a plasma cortisol level that is effective in the basal state or during uncomplicated anesthetic and surgical procedures may be inadequate in the setting of increased stress from prolonged or complicated surgical procedures or intercurrent infectious or inflammatory conditions.

Time course of HPA suppression

Because the minimal time that can produce HPA suppression cannot be estimated from the few well-documented cases available, estimates have been made based on adrenocortical weight and the adrenocortical response to provocative tests. The authors of a well-designed study in which normal subjects served as their own controls found an abnormal plasma cortisol response to ACTH and to insulin-induced hypoglycemia after a 5-day course of prednisone 25 mg twice daily, at 8 AM and 4 PM (Fig. 1) [29]. In another study, abnormal responsiveness to ACTH was seen after 3 days of

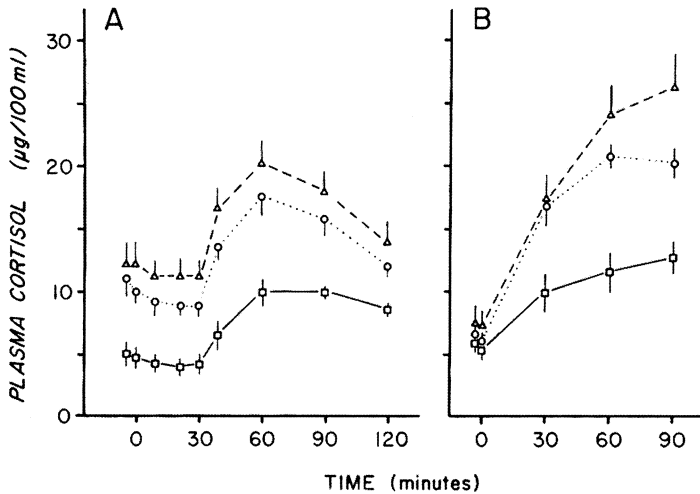


Fig. 1. Plasma cortisol response (mean \pm SEM) to (A) insulin-induced hypoglycemia and (B) synthetic ACTH in 10 subjects before (Δ) and 2 (\square) and 5 (\circ) days after conclusion of a 5 day course of prednisone 25 mg twice daily. (From Streck WF, Lockwood DH. Pituitary adrenal recovery following short-term suppression with corticosteroids. *Am J Med* 1979; 66:910–4; with permission.)

treatment [30]. As a general rule, any patient who has received a glucocorticoid in doses equivalent to at least 20 mg a day of prednisone for more than 5 days is at risk for HPA suppression. If the doses are closer to but above the physiologic range, 1 month is probably the minimal interval [4]. There is no risk for HPA suppression in patients who have received only replacement doses (no more than 25 mg of hydrocortisone, 5 mg prednisone, 4 mg triamcinolone, or 0.75 mg dexamethasone) as long as the glucocorticoid was given early in the day [31]. If doses are given late in the day, HPA suppression may occur as a consequence of inhibiting the diurnal surge of ACTH release [4].

In a study of the responses to corticotropin-releasing hormone (CRH) in patients on long-term glucocorticoid therapy there was an inverse but poor correlation between the dosage and duration of therapy and the plasma cortisol response to CRH [24]. Statistical analysis suggested an effect of unidentified factors. Whereas the daily glucocorticoid doses were constant for at least 1 week before the study and an estimate of cumulative doses was made, this study did not determine the daily dose in the year before the study. This may be one of the unidentified factors in question, possibly the most important one, accounting for the weakness of the correlation. This study did not compare the response to CRH with the response to ACTH or to a physiologic stimulus such as general anesthesia and surgery. The dose and duration of therapy can be used to identify patients at risk for HPA suppression but do not identify such patients with certainty.

Time course of recovery from HPA suppression

The time course of recovery from prolonged exposure to high doses of glucocorticoids was well described by Graber et al [32] in a classic study in 1965. They investigated the time course of recovery of pituitary and adrenocortical function in eight patients with Cushing's syndrome caused by an adrenocortical tumor and six patients who had received exogenous glucocorticoids in pharmacologic doses for 1 to 10 years. The findings in four of these patients are presented in Fig. 2. After the adrenocortical tumor had been removed or the exogenous steroids were discontinued, plasma 17-hydroxycorticosteroid levels and plasma ACTH levels were determined periodically at 6 AM for a prolonged period.

- In the first month after withdrawal of glucocorticoids, patients had mild symptoms of adrenal insufficiency, subnormal plasma (and also urinary) 17-hydroxycorticosteroids, abnormal responses to exogenous ACTH, and plasma ACTH concentrations that were inappropriately low in response to the subnormal plasma 17-hydroxycorticosteroid levels. Thus, the patients had diminished responses of the pituitary gland and the adrenal cortex.
- From the second to the fifth month after withdrawal of glucocorticoids, plasma ACTH levels returned to normal and in most cases to super-normal values, but the plasma 17-hydroxycorticosteroids and the responses to ACTH remained low. Also, the plasma ACTH levels exhibited a normal diurnal rhythm in the face of subnormal plasma 17-hydroxysteroid levels. In short, the adrenal cortex displayed an

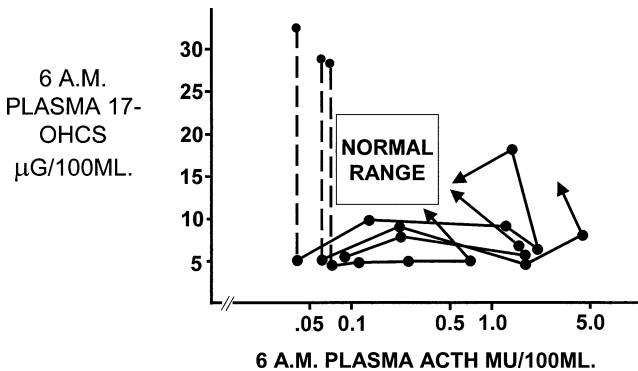


Fig. 2. Serial measurements of plasma 17-hydroxycorticosteroids (17-OHCS) and ACTH in four patients who had undergone prolonged pituitary suppression. Each patient is represented by a line. Each dot represents a measurement of plasma 17-hydroxycorticosteroids and ACTH, separated from the preceding measurement by at least 1 month. The broken lines represent the period during which adrenal tumors were removed and exogenous corticosteroids were withdrawn. (From Graber AL, Ney RL, Nicholson WE, et al. Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids. *J Clin Endocrinol Metab* 1965;25:11–6; with permission.)

impaired response to normal or elevated ACTH levels. Thus, pituitary function returned before adrenocortical function.

- From the sixth to the ninth month after withdrawal of glucocorticoids, plasma and urine 17-hydroxycorticosteroids returned to normal but in some patients normal 17-hydroxycorticosteroids were achieved in response to elevated ACTH levels. Thus, adrenocortical responsiveness was still impaired.
- Nine months or more after withdrawal of glucocorticoids, plasma and urinary 17-hydroxycorticosteroid levels, plasma ACTH levels and responses to provocative tests with ACTH and metyrapone were all normal.

Shortly thereafter, Livanou et al [33] investigated the response of the plasma 11-hydroxycorticosteroid level to insulin-induced hypoglycemia in patients who had received glucocorticoid therapy. They observed a progressive improvement in responsiveness from the time of cessation of glucocorticoids. Normal responses were observed after 1 year.

These studies describe the time course of recovery after prolonged courses of glucocorticoid therapy. Recovery from shorter courses of treatment occurs more rapidly.

For example, recovery from HPA suppression that has been induced by a brief course of glucocorticoids (25 mg of prednisone twice daily for 5 days) occurs within 5 days (Fig. 1) [29]. Comparable results have been recorded in other studies in children [34] and adults [35]. Patients with mild suppression of the HPA axis (defined as normal basal plasma and urine corticosteroid levels but impaired responses to ACTH and insulin-induced hypoglycemia) achieve normal function more rapidly than patients with severe depression of the HPA axis (defined as low basal plasma and urine corticosteroid levels and impaired responses to ACTH and insulin-induced hypoglycemia) [36]. The time course of recovery is a function of the dose and duration of previous glucocorticoid therapy [36–38].

It is often not possible from the information obtained in groups of well studied patients to predict the duration of recovery from a prolonged course of glucocorticoid therapy in an individual patient, especially when, as is often the case, the glucocorticoid dose has not been constant and therapy may have been intermittent. In such circumstances, persistence of HPA suppression should be considered for 12 months following cessation of glucocorticoid therapy.

In evaluating the risk that a patient has HPA suppression it is not sufficient to consider only the patient's current dose. One must review the patient's use of glucocorticoids during the previous year by looking at doses used and duration of therapy before applying the guidelines stated above. In the preoperative patient at risk for HPA suppression, additional assessment may be needed. (See section entitled, "Preoperative assessment of adrenocortical function.")

Management of HPA suppression from glucocorticoid therapy

In some circumstances it would be desirable to accelerate recovery from HPA suppression caused by glucocorticoid therapy in anticipation of general anesthesia and surgery. Unfortunately, there is no known way to accelerate recovery once it has been induced. ACTH injections do not prevent or reverse this process [4]. Conversion from daily glucocorticoid therapy in divided doses to alternate day glucocorticoid therapy (see later in the discussion) does not accelerate recovery, although it does permit recovery to occur. In children, an alternate day regimen may delay recovery [39], which otherwise occurs more rapidly than in adults [40].

Recovery from glucocorticoid-induced HPA suppression is time dependent and spontaneous. The rate of recovery is a function of the doses administered before tapering is begun [36–38] and while the dose is being reduced. Once the glucocorticoid has been stopped, withdrawal symptoms may be alleviated by small doses of hydrocortisone (10–20 mg) or prednisone (2.5–5 mg) in the morning. This approach may permit recovery to occur because it should not inhibit the nocturnal increase of ACTH levels, although some retardation of recovery has not been excluded.

Exogenous ACTH and the HPA system

Repeated administration of ACTH for a putative therapeutic purpose increases the cortisol secretory rate and increases plasma cortisol levels. One might expect that the elevated plasma cortisol levels would suppress endogenous ACTH release, resulting in secondary adrenal insufficiency, but the evidence does not support this hypothesis [4]. The inability of exogenous ACTH to cause secondary adrenal insufficiency is not attributable to the dose of ACTH administered, the frequency of its injection, the time of injection, or the plasma cortisol pattern following administration [41]. Daily ACTH administration causes bilateral adrenocortical hyperplasia. Possibly, the hyperplastic adrenal cortical tissue is accompanied by enhanced responsiveness to endogenous and exogenous ACTH. Whereas the threshold level of adrenocortical responsiveness is not increased in patients on daily ACTH injections [41], overall responsiveness may be enhanced (ie, the dose response curve may be shifted to the left). The preserved response of the adrenal cortex to ACTH may also reflect the fact that ACTH administration reduces the endogenous rate of ACTH secretion but not the total quantity secreted [42]. In contrast, glucocorticoids reduce the rate of ACTH secretion and the total amount secreted [42].

In general, ACTH injections offer no benefit over glucocorticoid therapy for therapeutic purposes and have several disadvantages [4,5]. ACTH is indicated for diagnosis (ie, the assessment of adrenocortical function). Whereas the therapeutic use of ACTH has declined in recent years, one still

occasionally encounters patients treated with ACTH injections with therapeutic intent.

Alternate day glucocorticoid therapy and the HPA system

Alternate day glucocorticoid therapy is a therapeutic approach designed to minimize the adverse effects of glucocorticoids while preserving therapeutic efficacy [4,5,43]. In this approach a short acting glucocorticoid (such as prednisone, prednisolone, or methylprednisolone) is given by mouth every 48 hours in the morning at about 8 AM. Patients treated in this manner may have some suppression of basal cortisol levels but have normal or nearly normal responses to provocative tests of adrenocortical function including the CRH stimulation test, ACTH stimulation tests, insulin-induced hypoglycemia, and a metyrapone test [4,44]. They experience less suppression than patients receiving daily therapy in comparable doses during each 48-hour period. Many patients who are receiving alternate day glucocorticoid therapy have previously taken daily therapy in divided doses. An accurate assessment of the risk for HPA suppression must take into account, especially during the previous 12-month period, not only the current regimen but also previous regimens.

Preoperative assessment of adrenocortical function

In the preoperative assessment of a glucocorticoid-treated patient, it is sometimes helpful to assess the adequacy of adrenocortical function. This assessment is necessary only if it will affect management. For example, a glucocorticoid-treated patient may have a condition caused or exacerbated by steroids, such as an upper gastrointestinal hemorrhage or a bowel perforation, which might otherwise benefit from rapid taper and cessation of the glucocorticoid. Preoperative assessment would not be necessary in a patient for whom interruption of steroid therapy is not tolerated (eg, because of the activity of the underlying disease or the need for immunosuppressive therapy in the recipient of a transplanted organ).

The short ACTH (cosyntropin, α_{1-24} corticotropin, Cortrosyn [Organon Canada Ltd., Toronto, Ontario, Canada], Synacthen [Novartis International AG, Basel, Switzerland]) stimulation test is a reliable means of assessing adrenocortical function preoperatively (Table 1) [14,15,22,25,45–48]. Whereas this test assesses directly only adrenocortical responsiveness, it is nevertheless a reliable guide to the integrity of the entire HPA axis. Because hypothalamic–pituitary function returns before adrenocortical function following cessation of glucocorticoids (see above), a normal response to ACTH indicates normal hypothalamic–pituitary function also. This deduction is supported by systematic observations. The plasma cortisol response to exogenous ACTH preoperatively corresponds to the maximal

Table 1
Short ACTH stimulation test

| | |
|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Method | Withhold exogenous glucocorticoids for 24 hours Give cosyntropin 250 µg as intravenous bolus or intramuscular injection Measure plasma cortisol 30 or 60 minutes after injection ^a |
| Interpretation | Normal response: plasma cortisol level > 18 µg/dL at 30 or 60 minutes |

^a The peak plasma cortisol level is the most reliable means of assessing HPA function in the short ACTH stimulation test [45–47]. Baseline plasma cortisol values are unnecessary and may be misleading in sick patients with a normal HPA axis, in whom stress may increase the baseline plasma value due to an increase in endogenous ACTH levels. This may reduce the increment between baseline and stimulated values [46].

Data from Refs. [45–47].

plasma cortisol level measured during the induction of general anesthesia and surgery in glucocorticoid-treated patients studied without preoperative or intraoperative steroid coverage [14,15,25,48]. A normal response to ACTH before surgery is unlikely to be followed by an abnormal response during general anesthesia and surgery [25]. On the other hand, an abnormal response to ACTH preoperatively is not always followed by clinical features of adrenal insufficiency during surgery. Some patients with an abnormal response to ACTH tolerate general anesthesia and surgery without perioperative glucocorticoid treatment [9,25].

Other tests of HPA function are not indicated. The low dose (1 µg) short ACTH test is more sensitive than the conventional dose (250 µg) short ACTH test in glucocorticoid-treated patients. The conventional test results in circulating ACTH levels that are well above the physiologic range. These nonphysiologic levels may engender a normal plasma cortisol response in patients with partial adrenocortical insufficiency. The low dose test, however, has not been characterized well enough to replace the conventional short ACTH test [49]. The lower limit of the normal range of plasma cortisol responses has not yet been determined. Moreover, there is no commercially available preparation of ACTH for the low dose test. The need to perform serial dilutions to prepare the agent is inconvenient and a potential source of error. For these reasons, the low dose short ACTH test cannot be recommended at this time. Insulin-induced hypoglycemia and the CRH stimulation test provide no advantage over the short ACTH test [5].

Perioperative management

Which glucocorticoid-treated patients need perioperative glucocorticoid coverage? In general, coverage should be provided to the following patients:

- Those who have impaired responsiveness to a test of adrenocortical reserve, such as the short ACTH stimulation test, and those with the

following features who need surgery urgently before an ACTH test can be performed:

- Those who have clinical findings of Cushing's syndrome
- Those who have otherwise unexplained findings consistent with adrenocortical insufficiency, such as hypotension, hyponatremia, hyperkalemia, and eosinophilia
- Those who are at risk for HPA suppression and adrenal insufficiency based on our knowledge of the doses and duration of glucocorticoid therapy that may cause these conditions. (See earlier: "Time course of ACTH suppression" and "Time course of recovery from HPA suppression").

How much glucocorticoid therapy is needed for perioperative coverage of the patient with proven or suspected HPA suppression? Shortly after the introduction of glucocorticoid agents into clinical practice in the late 1940s, patients were described who developed adrenocortical insufficiency following perioperative withdrawal of glucocorticoid therapy [4,9]. In response to the need for an approach to the management of glucocorticoid-treated patients during surgery, arbitrary guidelines were proposed, based on assumptions that were, in retrospect, invalid [9]. Consequently, for decades physicians used large doses of glucocorticoids on the day of surgery, ranging from 300 to 1000 mg of hydrocortisone per day or equivalent, with prolonged tapers lasting days or even weeks. Studies over the last 3 decades provide a rational basis for revised guidelines, based on an improved knowledge of the normal adrenocortical response to the stress of general anesthesia and surgery, and on studies of various glucocorticoid regimens in this clinical situation.

The normal cortisol secretory rate in response to general anesthesia and surgery is about 75 to 150 mg a day; it rarely exceeds 200 mg a day [9,22]. The cortisol secretory rate in response to minor procedures is about 50 mg a day [9,22]. The cortisol secretory rate seems to be a function of the duration and the magnitude of the surgical procedure. There is no evidence that larger glucocorticoid doses are needed.

Informative studies of perioperative steroid regimens are available. In a classic study, bilateral adrenalectomy was performed in cynomolgus monkeys, which were then treated with replacement glucocorticoid (hydrocortisone) and mineralocorticoid doses for 4 months [50]. The adrenalectomized monkeys then received three different regimens of glucocorticoid coverage for four days before surgery cholecystectomy, while mineralocorticoid replacement continued. One group received a normal replacement dose, one group received one-tenth that dose, and one group received 10 times that dose. The animals in the group that received one-tenth the normal dose had hypotension, decreased peripheral vascular resistance, and an increased mortality rate following surgery. The group receiving the normal replacement dose displayed no difference in postoperative complications

from the group that received ten times the normal dose. This study indicates that in cynomolgous monkeys with adrenal insufficiency, replacement doses of glucocorticoids provide satisfactory perioperative coverage. A small double blind study in humans provides comparable results [51]. Patients in the study had taken at least 7.5 mg a day of prednisone for several months and had an abnormal response to an ACTH test. On the day of surgery, all patients received their usual daily dose of prednisone. One subgroup of 12 patients received saline perioperatively, and the other subgroup of 6 patients received hydrocortisone in saline intravenously at doses of 100 mg one hour before surgery, 25 mg every 6 hours for 2 days, and then 25 mg every 12 hours for 1 day. There was no significant difference in outcome between the two groups. This study suggests that patients with adrenal suppression from glucocorticoid therapy do not experience hypotension or tachycardia when given their usual daily dose of glucocorticoids while undergoing surgical procedures such as joint replacements and abdominal surgery [51].

Specific recommendations

A multidisciplinary group has made recommendations based on the following conclusions: (1) perioperative glucocorticoid coverage should only provide a quantity equivalent to the normal physiologic response to surgical stress, and (2) the risk of anesthesia and surgery in glucocorticoid treated patients who undergo surgery without coverage is a function of the duration and severity of the surgical procedure (Table 2) [9].

Table 2
Recommendations for perioperative glucocorticoid coverage

| Degree of surgical stress | Definition | Glucocorticoid dose |
|---------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Minor | Procedure under local anesthesia and less than one hour in duration (eg, inguinal hernia repair) | Hydrocortisone 25 mg or equivalent |
| Moderate | Procedure such as vascular surgery of a lower extremity or a total joint replacement | Hydrocortisone 50–75 mg or equivalent This could be continuation of usual daily steroid dose (eg, prednisone 10 mg a day) and hydrocortisone 50 mg intravenously during surgery |
| Major | Procedure such as esophagogastrectomy or operation on cardiopulmonary bypass | Usual glucocorticoid (eg, prednisone 40 mg or the parenteral equivalent within 2 h before surgery) and hydrocortisone 50 mg intravenously every 8 h after the initial dose for the first 48 to 72 h of the postoperative period |

Adapted from Salem M, Tainsh RE Jr, Bromberg J, et al. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 1994;219:416–25.

The recommendations are expressed as doses of hydrocortisone. This agent has mineralocorticoid activity at doses above approximately 100 mg per day. As explained earlier, patients with glucocorticoid-induced secondary adrenal insufficiency do not have mineralocorticoid (aldosterone) deficiency. The mineralocorticoid activity of hydrocortisone may produce undesirable side effects including fluid retention, edema, and hypokalemia. Thus, it is preferable to use a glucocorticoid without mineralocorticoid activity when treating patients with this condition, especially when the total dose of hydrocortisone exceeds 100 mg per day. Methylprednisolone is a satisfactory alternative for this purpose. Methylprednisolone 4 mg is equivalent to hydrocortisone 20 mg.

Postoperatively, glucocorticoid doses should not be tapered inadvertently to a level below that known to control the underlying disease for which the steroids are needed.

Summary

HPA suppression is a common consequence of glucocorticoid therapy, whereas overt secondary adrenal insufficiency is a rare but life-threatening condition. Prolonged hypotension and a response to adequate doses of a glucocorticoid agent are not reliable ways to assess adrenocortical function. One must also demonstrate plasma cortisol levels that are inappropriately low for the clinical situation. Hypotension in patients previously treated with glucocorticoids is caused by loss of the permissive effect of glucocorticoids on vascular tone, which may be related in turn to enhanced PGI₂ production in the absence of glucocorticoids. It is not caused by mineralocorticoid deficiency. Recurrent problems of study design and interpretation have plagued this area of investigation. Any patient who has received a glucocorticoid in doses equivalent to at least 20 mg a day of prednisone for more than 5 days is at risk for HPA suppression. If the doses are closer to but above the physiologic range, 1 month is probably the minimal interval. Recovery from prolonged exposure to high doses of glucocorticoids may take up to 1 year. Pituitary function returns before adrenocortical function. Recovery from short courses of treatment (eg, 5 days) occurs more rapidly, in about 5 days. Recovery is time-dependent and spontaneous. The rate of recovery is a function of the dose and duration of therapy before tapering is started and while the dose is being reduced. ACTH therapy does not cause adrenocortical suppression but offers no advantage over glucocorticoids, has several disadvantages, and should no longer be used. Patients on alternate day glucocorticoid therapy have some suppression of basal cortisol levels but have normal or nearly normal responses to provocative tests of adrenocortical function. The standard short ACTH stimulation test is a reliable means of assessing adrenocortical function preoperatively. The low dose (1 µg) short ACTH test is promising

but has not been sufficiently well characterized, requires serial dilutions and cannot be recommended at this time. Studies of the physiologic adrenocortical response to surgical stress provide a basis for revised dose recommendations for perioperative coverage in the patient with known or suspected HPA suppression. Recommendations of a multidisciplinary group are presented.

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References

- [1] Polley HF, Slocumb CH. Behind the scenes with cortisone and ACTH. *Mayo Clin Proc* 1976;51:471–7.
- [2] Hench PS, Kendall EC, Slocumb CH, et al. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis. *Proc Staff Meet Mayo Clin* 1949;24:181–97.
- [3] Hench PS, Slocumb CH, Polley HF, et al. Effect of cortisone and pituitary adrenocorticotrophic hormone (ACTH) on rheumatic diseases. *JAMA* 1950;144:1327–35.
- [4] Axelrod L. Glucocorticoid therapy. *Medicine (Baltimore)* 1976;55:39–65.
- [5] Axelrod L. Corticosteroid therapy. In: Becker KL, editor. *Principles and Practice of Endocrinology and Metabolism*. 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 751–64.
- [6] Scott–Levin SPA. 12/01, Newton, PA (source): Top 200 brand-name drugs by units in 2001. *Drug Topics* 2002;5:38.
- [7] Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy. A systematic review and meta-analysis. *Arch Intern Med* 1999;159:941–55.
- [8] Nylén E, Zaloga GP, Becker KL, et al. Endocrine therapeutics in critical illness. In: Becker KL, editor. *Principles and Practice of Endocrinology and Metabolism*, 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 2108–21.
- [9] Salem M, Tainsh Jr RE, Bromberg J, et al. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. *Ann Surg* 1994;219:416–25.
- [10] Kehlet H, Binder C. Adrenocortical function and clinical course during and after surgery in unsupplemented glucocorticoid treated patients. *Br J Anaesth* 1973;45:1043–8.
- [11] Mattingly D, Tyler C. Plasma 11-hydroxycorticoid levels in surgical stress. *Proc R Soc Med* 1965;58:1010–2.
- [12] Cope CL. The adrenal cortex in internal medicine. Part I. *Br Med J* 1966;2:847–53.
- [13] Sampson PA, Brooke BN, Winstone NE. Biochemical confirmation of collapse due to adrenal failure. *Lancet* 1961;1:1377.
- [14] Jasani MK, Freeman PA, Boyle JA, et al. Studies of the rise in plasma 11-hydroxycorticosteroids (11-OHCS) in corticosteroid-treated patients with rheumatoid arthritis during surgery: Correlations with the functional integrity of the hypothalamo-pituitary-adrenal axis. *Q J Med* 1968;37:407–21.
- [15] Sampson PA, Winstone NE, Brooke BN. Adrenal function in surgical patients after steroid therapy. *Lancet* 1962;2:322–5.
- [16] Axelrod L. Inhibition of prostacyclin production mediates permissive effect of glucocorticoids on vascular tone. Perturbations of this mechanism contribute to pathogenesis of Cushing's syndrome and Addison's disease. *Lancet* 1983;1:904–6.

- [17] Rascher W, Dietz R, Schömig A, et al. Modulation of sympathetic vascular tone by prostaglandins in corticosterone-induced hypertension in rats. *Clin Sci* 1979;57:235s–7s.
- [18] Rascher W, Dietz R, Schömig A, et al. Reversal of corticosterone-induced supersensitivity of vascular smooth muscle to noradrenaline by arachidonic acid and prostacyclin. *Eur J Pharmacol* 1980;68:267–73.
- [19] Mohler JL, Michael KA, Freedman AM, et al. The evaluation of postoperative function of the adrenal gland. *Surg Gynecol Obstet* 1985;161:551–6.
- [20] Alford Jr WC, Meador CK, Mihalevich J, et al. Acute adrenal insufficiency following cardiac surgical procedures. *J Thorac Cardiovasc Surg* 1979;78:489–93.
- [21] Kaalund Jensen J, Elb S. Preoperative and postoperative complications in previously corticosteroid-treated patients. *Nord Med* 1966;25:978.
- [22] Kehlet H. Clinical course and hypothalamic-pituitary-adrenocortical function in glucocorticoid-treated surgical patients. Copenhagen: FADL's Forlag, 1976.
- [23] Christy NP. Iatrogenic Cushing's syndrome. In: Christy NP, editor. *The Human Adrenal Cortex*. New York, Harper & Row; 1971. p. 395–425.
- [24] Schlaghecke R, Kornely E, Santen RT, et al. The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin-releasing hormone. *N Engl J Med* 1992;326:226–30.
- [25] Kehlet H, Binder C. Value of an ACTH test in assessing hypothalamic-pituitary-adrenocortical function in glucocorticoid-treated patients. *Br Med J* 1973;2:147–9.
- [26] Knudsen L, Christiansen LA, Lorentzen JE. Hypotension during and after operation in glucocorticoid-treated patients. *Br J Anaesth* 1981;53:295–301.
- [27] Plumpton FS, Besser GM, Cole PV. Corticosteroid treatment and surgery. 1. An investigation of the indications for steroid cover. *Anaesthesia* 1969;24:3–11.
- [28] Bornstein SR, Chrousos GP. The hypothalamic-pituitary-adrenal axis in stress and critical illness. In: Becker KL, editor. *Principles and Practice of Endocrinology and Metabolism*, 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 2087–94.
- [29] Streck WF, Lockwood DH. Pituitary adrenal recovery following short-term suppression with corticosteroids. *Am J Med* 1979;66:910–4.
- [30] Christy NP, Wallace EZ, Jailer JW. Comparative effects of prednisone and of cortisone in suppressing the response of the adrenal cortex to exogenous adrenocorticotropin. *J Clin Endocrinol Metab* 1956;16:1059–74.
- [31] Danowski TS, Bonessi JV, Sabeh G, et al. Probabilities of pituitary-adrenal responsiveness after steroid therapy. *Ann Intern Med* 1964;61:11–26.
- [32] Graber AL, Ney RL, Nicholson WE, et al. Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids. *J Clin Endocrinol Metab* 1965;25:11–6.
- [33] Livanou T, Ferriman D, James VHT. Recovery of hypothalamo-pituitary-adrenal function after corticosteroid therapy. *Lancet* 1967;2:856–9.
- [34] Zora JA, Zimmerman D, Carey TL, et al. Hypothalamic-pituitary-adrenal axis suppression after short-term, high-dose glucocorticoid therapy in children with asthma. *J Allergy Clin Immunol* 1986;77:9–13.
- [35] Carella MJ, Srivastava LS, Gossain VV, et al. Hypothalamic-pituitary-adrenal function one week after a short burst of steroid therapy. *J Clin Endocrinol Metab* 1993;76:1188–91.
- [36] Spitzer SA, Kaufman H, Koplovitz A, et al. Beclomethasone dipropionate and chronic asthma. The effect of long-term aerosol administration on the hypothalamic-pituitary-adrenal axis after substitution for oral therapy with corticosteroids. *Chest* 1976;70:38–42.
- [37] Westerhof L, VanDitmars MJ, DerKinderen PJ, et al. Recovery of adrenocortical function during long-term treatment with glucocorticoids. *Br Med J* 1970;4:534–7.
- [38] Westerhof L, vanDitmars MJ, DerKinderen PJ, et al. Recovery of adrenocortical function during long-term treatment with glucocorticoids. *Br Med J* 1972;2:195–7.
- [39] Morris HG, Neuman I, Ellis EF. Plasma steroid concentrations during alternate-day treatment with prednisone. *J Allergy Clin Immunol* 1974;54:350–8.

- [40] Morris HG, Jorgensen JR. Recovery of endogenous pituitary-adrenal function in corticosteroid-treated children. *J Pediatr* 1971;79:480–8.
- [41] Carter ME, James VHT. Comparison of effects of corticotrophin and corticosteroids on pituitary-adrenal function. *Ann Rheum Dis* 1971;30:91–7.
- [42] Daly JR, Fletcher MR, Glass D, et al. Comparison of effects of long-term corticotrophin and corticosteroid treatment on responses of plasma growth hormone, ACTH, and corticosteroid to hypoglycaemia. *Br Med J* 1974;2:521–4.
- [43] Harter JG, Reddy WJ, Thorn GW. Studies on an intermittent corticosteroid dosage regimen. *N Engl J Med* 1963;269:591–6.
- [44] Schürmeyer TH, Tsokos GC, Avgerinos PC, et al. Pituitary-adrenal responsiveness to corticotropin-releasing hormone in patients receiving chronic, alternate day glucocorticoid therapy. *J Clin Endocrinol Metab* 1985;61:22–7.
- [45] Lindholm JL, Kehlet H. Re-evaluation of the clinical value of the 30 min ACTH test in assessing the hypothalamic-pituitary-adrenocortical function. *Clin Endocrinol* 1987;26:53–9.
- [46] May ME, Carey RM. Rapid adrenocorticotrophic hormone test in practice. A retrospective review. *Am J Med* 1985;79:679–84.
- [47] Nelson JC, Tindall Jr DJ. A comparison of the adrenal responses to hypoglycemia, metyrapone and ACTH. *Am J Med Sci* 1978;275:165–72.
- [48] Marks LJ, Donovan MJ, Duncan FJ, et al. Adrenocortical response to surgical operations in patients treated with corticosteroids or corticotropin prior to surgery. *J Clin Endocrinol Metab* 1959;19:1458–70.
- [49] Streeten DHP. Shortcomings in the low-dose (1 μ g) ACTH test for the diagnosis of ACTH deficiency states. *J Clin Endocrinol Metab* 1999;84:835–7.
- [50] Udelsman R, Ramp J, Gallucci WT, et al. Adaptation during surgical stress. A reevaluation of the role of glucocorticoids. *J Clin Invest* 1986;77:1377–81.
- [51] Glowniak JV, Loriaux DL. A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. *Surgery* 1997;121:123–9.