INTRODUCTION — Chronic glucocorticoid therapy can suppress the hypothalamic-pituitary-adrenal (HPA) axis and, during times of stress such as surgery, the adrenal glands may not respond appropriately. Protocols for "stress dose" steroids followed reports in the 1950s of possible surgery-associated adrenal insufficiency due to sudden preoperative withdrawal of glucocorticoids. However, recent studies have questioned both the need for and current dosage regimens of supplemental perioperative glucocorticoids [1-3].

In addition to HPA axis suppression, chronic glucocorticoid therapy may cause a number of other problems in the perioperative period:

- Impaired wound healing [4]
- Increased friability of skin, superficial blood vessels, and other tissues (eg, mild pressure may cause hematoma or skin ulceration, removing adhesive tape may tear the skin, and sutures may tear the gut wall)
- Increased risk of fracture, infections, gastrointestinal hemorrhage, or ulcer [5,6]. (See "Major side effects of systemic glucocorticoids").

The management of the surgical patient on chronic glucocorticoid therapy is reviewed here. Perioperative glucocorticoid regimens for patients taking replacement glucocorticoid for primary adrenal insufficiency are addressed separately. (See "Treatment of adrenal insufficiency").

CORTISOL SECRETION DURING STRESS — Acute physical or psychological stress activates the HPA axis, resulting in increased plasma corticotropin (ACTH) and serum cortisol concentrations. Stress exerts its effects by stimulating the hypothalamus to release ACTH secretagogues, with corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) being the most important [7,8]. (See "ACTH and cortisol secretion in health and disease").

Surgery is one of the most potent activators of the HPA axis. Plasma ACTH concentrations increase at...
the time of incision and during surgery, but the greatest ACTH and cortisol secretion occurs during reversal of anesthesia, extubation, and in the immediate postoperative recovery period, primarily it appears, in response to pain [9,10]. The response is mediated by afferent nerve impulses, since it can be abolished by interrupting the neural connections from the operative site, such as by sectioning the spinal cord [11], epidural anesthesia [12], or local anesthesia. The plasma ACTH and serum cortisol responses to surgery can also be reduced by opiate drugs [10,13].

There is considerable variation in the increase in cortisol secretion among individuals undergoing surgery; this variability is in part due to concomitant medication use, age, and concurrent illness. In general, the adrenal gland produces about 50 mg/day of cortisol during a minor procedure or surgery (normal basal secretion is 8 to 10 mg/day), while 75 to 100 mg/day are produced with major surgery [14]. The cortisol secretion rate can reach 200 to 500 mg/day with severe stress, but secretion rates greater than 200 mg/day in the 24 hours after surgery are rare [2].

**Effect of exogenous glucocorticoids** — Both endogenous and exogenous glucocorticoids exert negative feedback control on the HPA axis by suppressing CRH secretion and, consequently, ACTH secretion. This leads to adrenal atrophy and loss of cortisol secretory capability.

*Prednisone* doses of less than 5 mg/day given in the morning do not suppress the HPA axis. Patients on doses of 5 mg/day or higher have considerable variability in HPA axis suppression that does not correlate well with age, sex, dose, or duration of therapy [15,16]. This variability is probably due to differences in rates of glucocorticoid metabolism (show figure 1). It can be assumed that equivalent morning dosages of other glucocorticoids (eg, 4 mg/day of methylprednisolone, 0.5 mg/day of dexamethasone, or 20 mg/day of hydrocortisone) have a similar effect. (show table 1). (See "Pharmacologic use of glucocorticoids").

The following patients can be considered not to have suppression of their hypothalamic-pituitary-adrenal axis:

- Any patient who has received any dose of glucocorticoid for less than three weeks.
- Patients who have received morning doses of less than 5 mg/day of prednisone or its equivalent.
- Patients treated with alternate-day glucocorticoid therapy [17-19].

In contrast, patients who should be assumed to have functional suppression of hypothalamic-pituitary-adrenal function include:

- Any patient who has received more than 20 mg/day of prednisone or its equivalent (eg, 16 mg/day of methylprednisolone, 2 mg/day of dexamethasone, or 80 mg/day of hydrocortisone) for more than three weeks [20].
- Any patient who has clinical Cushing's syndrome.

The intermediate categories of patients are more problematic; specific testing may be necessary to determine the presence of HPA axis suppression (see "Evaluation of HPA axis suppression" below).

**Inhaled and topical glucocorticoids** — Chronic use of inhaled or high potency topical glucocorticoids may also cause HPA axis suppression:

- A meta-analysis of 21 studies of urinary cortisol excretion and 13 studies of morning serum cortisol concentrations in patients taking inhaled glucocorticoids found evidence of HPA axis suppression that was most common with glucocorticoid doses greater than 0.8 mg/day, but was often absent even at higher doses [21]. HPA axis suppression was seen with lower doses of fluticasone than with beclomethasone, triamcinolone, or budesonide.
A new inhaled agent, **ciclesonide**, is hydrolyzed to its active metabolite, desisobutyryl-CIC (des-CIC), in the lungs, limiting systemic availability. A meta-review of four studies using the agent at doses of 160 to 640 mcg/d did not show evidence for suppression of morning or 24-hour urinary cortisol [22].

Class I topical glucocorticoids (the most potent) in doses as little as 2 g/day can cause significant HPA axis suppression [23,24]. In one report, temporary reversible HPA axis suppression was noted in 8 of 40 patients (20 percent) with psoriasis treated with superpotent topical glucocorticoid for three weeks or more [25]. Factors that predispose to HPA axis suppression include use of high potency glucocorticoids, chronic use, application to the scalp or intertriginous areas, treatment of large areas, occlusion with impermeable dressings, poor skin integrity, liver failure, and young age. (See "Pharmacologic use of glucocorticoids").

**EVALUATION OF HPA AXIS SUPPRESSION** — Patients taking 5 to 20 mg/day of **prednisone** or its equivalent for more than three weeks may or may not have suppression of the HPA axis. The patient who has discontinued glucocorticoids in the year prior to surgery presents another problem. Early studies found that profound suppression of the HPA axis could take up to one year to recover fully [26,27]. This led some to recommend the administration of glucocorticoids to any patient who had been on prednisone doses of more than 5 mg/day for more than one week in the 6 to 12 months prior to surgery, but this is clearly unwarranted. (See "Glucocorticoid withdrawal").

In patients whose HPA axis status is uncertain, one can give glucocorticoids perioperatively or, if time permits, test for the responsiveness of the adrenal to ACTH stimulation. (See "Evaluation of the response to ACTH in adrenal insufficiency"). A normal serum cortisol response to ACTH stimulation is predicated on the assumption that the adrenal gland has been stimulated with sufficient endogenous ACTH each day to prevent adrenal atrophy and to maintain the activity of the steroidogenic enzymes.

However, some have questioned whether the high-dose (250 microgram) ACTH stimulation test accurately predicts the ability of a patient to respond adequately to stress, since occasional patients have normal responses to ACTH, but subnormal serum cortisol responses to insulin-induced hypoglycemia (a sensitive measure of HPA axis suppression) [28,29]. Some studies found that the ACTH stimulation test predicted both the response to stress and surgical complications [30], but several subsequent reports have shown that patients who have laboratory evidence of HPA axis suppression may have a normal clinical response to surgical stress [1,31,32].

In a prospective study of 40 renal allograft recipients admitted with significant physiologic stress, including sepsis, metabolic abnormalities, and surgery, the patients received only their baseline **prednisone** (5 to 10 mg/day) and no stress doses of glucocorticoids [1]. The clinical course of the patients revealed no evidence of adrenal insufficiency. Five episodes of hyponatremia and seven instances of hypotension were attributed to primary disease processes and responded promptly to specific treatment without steroid supplementation. Biochemical evaluation during stress revealed suppression of the plasma ACTH concentration in 75 percent of episodes, elevation of urinary free cortisol excretion in 79 percent, and elevation of the serum cortisol concentration in 56 percent. These findings suggest that these patients had physiologically adequate adrenal function. The ACTH stimulation test overestimated the incidence and degree of clinically significant adrenal dysfunction (63 percent of patients) and was not a useful indication of a requirement for additional glucocorticoids.

In a study of 18 patients who had been taking at least 7.5 mg/day of prednisone for several months and had secondary adrenal insufficiency as defined by ACTH stimulation testing, the patients were randomly assigned to two groups: one group received perioperative injections of saline solution alone (n=12) and the other received perioperative saline solution and **hydrocortisone** (n=6) [31]. All patients received their usual daily prednisone dose throughout the study. Most subjects underwent major operations such as joint replacements and abdominal operations. One patient in each group had hypotension that resolved with volume replacement alone. The average pulse rates and blood pressures were similar in the two groups during the perioperative period.
Rare patients who respond normally to the high-dose ACTH test have a subnormal serum cortisol response to surgery [33]. Nevertheless, they tolerate surgery well [34], presumably because more than basal daily cortisol secretion is not necessary to survive surgery [35].

Thus, with one exception, any patient who responds normally to the high-dose ACTH test does not require glucocorticoid supplementation perioperatively. The exception is the patient who is acutely ACTH-deficient, as might occur soon after pituitary surgery [29]. In these cases the low-dose (1 microgram) ACTH stimulation test, insulin tolerance test or metyrapone stimulation test may detect adrenal insufficiency better than the high-dose test, and similar considerations perioperatively likely apply. (See "Diagnosis of adrenal insufficiency").

RECOMMENDATIONS — Several authors have recommended that patients on chronic glucocorticoids undergoing surgery receive only their usual daily dose of glucocorticoid perioperatively. These recommendations are based upon studies that have shown that no surgical patient who was treated with his usual steroid dose developed intraoperative or postoperative hypotension or any other perioperative signs of adrenal insufficiency [1,31,32]. However, the clinician may decide that even a small risk of adrenal insufficiency outweighs the risk of 24 to 48 hours of stress doses of glucocorticoid.

In general, patients who have taken any dose of glucocorticoids for less than three weeks or who have taken chronic alternate day therapy are unlikely to have a suppressed HPA axis and should continue on their usual dose of glucocorticoids perioperatively.

HPA axis suppression should be assumed to be present in patients taking prednisone at a dose greater than 20 mg/day for three weeks or more, and in patients with a Cushingoid appearance. Two groups suggested guidelines for glucocorticoid coverage in these individuals that takes into account the magnitude of the stress based upon type and duration of surgery, and the known glucocorticoid production rates associated with it (show table 2) [2,36]. However, a replacement dosage of glucocorticoid appears to be sufficient for most patients even during major surgery. If higher dosages are used, patients should revert to the usual replacement dose within 48 hours of surgery, unless other circumstances intervene.

Patients on intermediate doses of glucocorticoids should undergo testing. A normal response to cortrosyn, 250 ug, does not exclude adrenal insufficiency, but a subnormal response indicates adrenal suppression [37]. The low-dose ACTH stimulation test, insulin tolerance test or metyrapone stimulation test may be used to assess possible HPA axis suppression. (See "Diagnosis of adrenal insufficiency"). While these tests do not absolutely predict the stress response to surgery, it is generally safe to assume that patients who respond normally do not require increased doses of glucocorticoid perioperatively. The exception is the patient who is acutely ACTH-deficient, as might occur soon after pituitary surgery [29]. Patients with a subnormal response to the ACTH stimulation test should receive glucocorticoid (show table 1).

Physicians should be aware of the potential for subclinical adrenal suppression in any patient who has been using prolonged high-dose inhaled or topical glucocorticoids [21,23-25]. Nevertheless, it seems reasonable to withhold glucocorticoids in these patients unless they appear Cushingoid or exhibit signs or symptoms of adrenal insufficiency perioperatively.

Patients who are taking glucocorticoids should be monitored carefully for infection postoperatively, because glucocorticoids may suppress the fever response.

Use of UpToDate is subject to the Subscription and License Agreement.

REFERENCES
1. Bromberg, JS, Alfrey, EJ, Barker, CF, et al. Adrenal suppression and steroid supplementation in


25. Katz, HI, Hien, NT, Prawer, SE, et al. Superpotent topical steroid treatment of psoriasis vulgaris -


GRAPHICS

Prednisone metabolism toxicity

Prednisolone metabolism may influence side effects
Disappearance curves of tritiated prednisolone in five patients who did not develop side effects while taking prednisone and in eight who did. The patients who developed side effects cleared prednisolone from the circulation more slowly. Data from Kozower, M, Veatch, L, Kaplan, MM, J Clin Endocrinol Metab 1974; 38:407.

Corticosteroid preparations

Comparison of commonly corticosteroid preparations

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Approximate equivalent dose, mg</th>
<th>Relative potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>20</td>
<td>1.0</td>
</tr>
<tr>
<td>Cortisone</td>
<td>25</td>
<td>0.8</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
<td>4.0</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>4.0</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4</td>
<td>5.0</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>30-150</td>
</tr>
</tbody>
</table>

Corticosteroid coverage surgery

Corticosteroid coverage for surgery in patients taking exogenous corticosteroids
For minor procedures or surgery under local anesthesia (eg, inguinal hernia repair) take usual morning steroid dose. No extra supplementation is necessary.

For moderate surgical stress (eg, lower extremity revascularization, total joint replacement) take usual morning steroid dose. Give 50 mg hydrocortisone intravenously just before the procedure and 25 mg of hydrocortisone every 8 hours for 24 hours. Resume usual dose thereafter.

For major surgical stress (eg, esophagogastrectomy, total proctocolectomy) take usual am steroid dose. Give 100mg of intravenous hydrocortisone before induction of anesthesia, and 50mg every 8 hours for 24 hours. Taper dose by half per day to maintenance level.