Review Article

Drug Therapy

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CORTICOSTEROID THERAPY IN SEVERE ILLNESS

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SEVERE illnesses, trauma, anesthesia, and surgery are accompanied by activation of the hypothalamic–pituitary–adrenal axis, as demonstrated by increased serum corticotropin and cortisol concentrations.[1-7] This activation is an essential component of the general adaptation to stress and contributes to the maintenance of homeostasis.[8] The efficacy of replacement doses or high doses of corticosteroids in patients with severe illness, especially those with multiorgan-system diseases, is uncertain.[9-12] The uncertainty is even greater in patients who are already taking corticosteroids. Standard therapy for the latter patients consists of the administration of high doses of corticosteroids during any severe illness and perioperatively. We review here the value of corticosteroid administration during severe illness in patients with normal hypothalamic–pituitary–adrenal function and in patients receiving corticosteroid treatment or replacement therapy before the illness.

EFFECT OF CORTICOSTEROIDS ON CIRCULATORY ASPECTS OF THE STRESS RESPONSE

Cortisol has a vital supportive role in the maintenance of vascular tone, endothelial integrity, vascular permeability, and the distribution of total body water within the vascular compartment.[13-15] It also potentiates the vasoconstrictor actions of catecholamines.[13,14] Adrenalectomy predisposes animals to hypovolemic and laparotomy-induced circulatory shock,[16,17] which can be prevented by replacement doses of corticosteroids.[18]

In humans, chronic adrenal deficiency is characterized by decreased systemic vascular resistance and decreased cardiac contractility. However, a variety of hemodynamic abnormalities have been described during acute adrenal insufficiency. They include hypovolemic shock (decreased preload, depressed myocardial contractility, and increased systemic vascular resistance)[19,20] and hyperdynamic shock (high cardiac output and decreased systemic vascular resistance similar to those in septic shock).[20-24] These different hemodynamic findings may reflect the fact that some patients had already received some volume replacement before cardiovascular function was studied or that their mineralocorticoid secretion varied depending on whether they had primary or secondary adrenal insufficiency. One important conclusion is that hypotension in patients with adrenal insufficiency may mimic either hypovolemic or septic shock, a conclusion that emphasizes the need to include adrenal insufficiency in the differential diagnosis of both.[20]

THE NORMAL RESPONSE OF THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS TO CRITICAL ILLNESS AND THE CONCEPT OF RELATIVE ADRENAL INSUFFICIENCY

Pain, fever, and hypovolemia all result in a sustained increase in corticotropin and cortisol secretion.[8,25,26] During surgical procedures such as laparotomy, serum corticotropin and cortisol concentrations rise rapidly but usually return to base-line values within 24 to 48 hours[27,28] (Fig. 1A). The magnitude of the postoperative increase in serum cortisol concentrations is positively correlated with the extent of surgery.[29,31] As compared with the concentrations before surgery, mean serum cortisol concentrations measured for 24 hours beginning two days after surgery were increased by 84 percent after laparotomy, but by only 36 percent after less extensive procedures such as operations on the joints, breast, or neck ($P<0.005$).[32] After operation, there is initially no circadian variation in serum cortisol concentrations (Fig. 1A). During severe illness, serum cortisol concentrations tend to be even higher (Fig. 1B).[30,32-34] The values are highest in patients with the highest illness-severity scores[3,5,7,30,32-35] and in those with the highest mortality,[5] and the values are very high (30 to 260 μg per deciliter [828 to 7173 nmol per liter]) shortly before death.[36]

Adrenal function in severely ill patients is often evaluated by a corticotropin-stimulation test, in which serum cortisol is measured at base line and 30 to 60 minutes after the intravenous administration of 250 μg of cosyntropin. The interpretation of the responses is difficult in seriously ill patients, however. Se-

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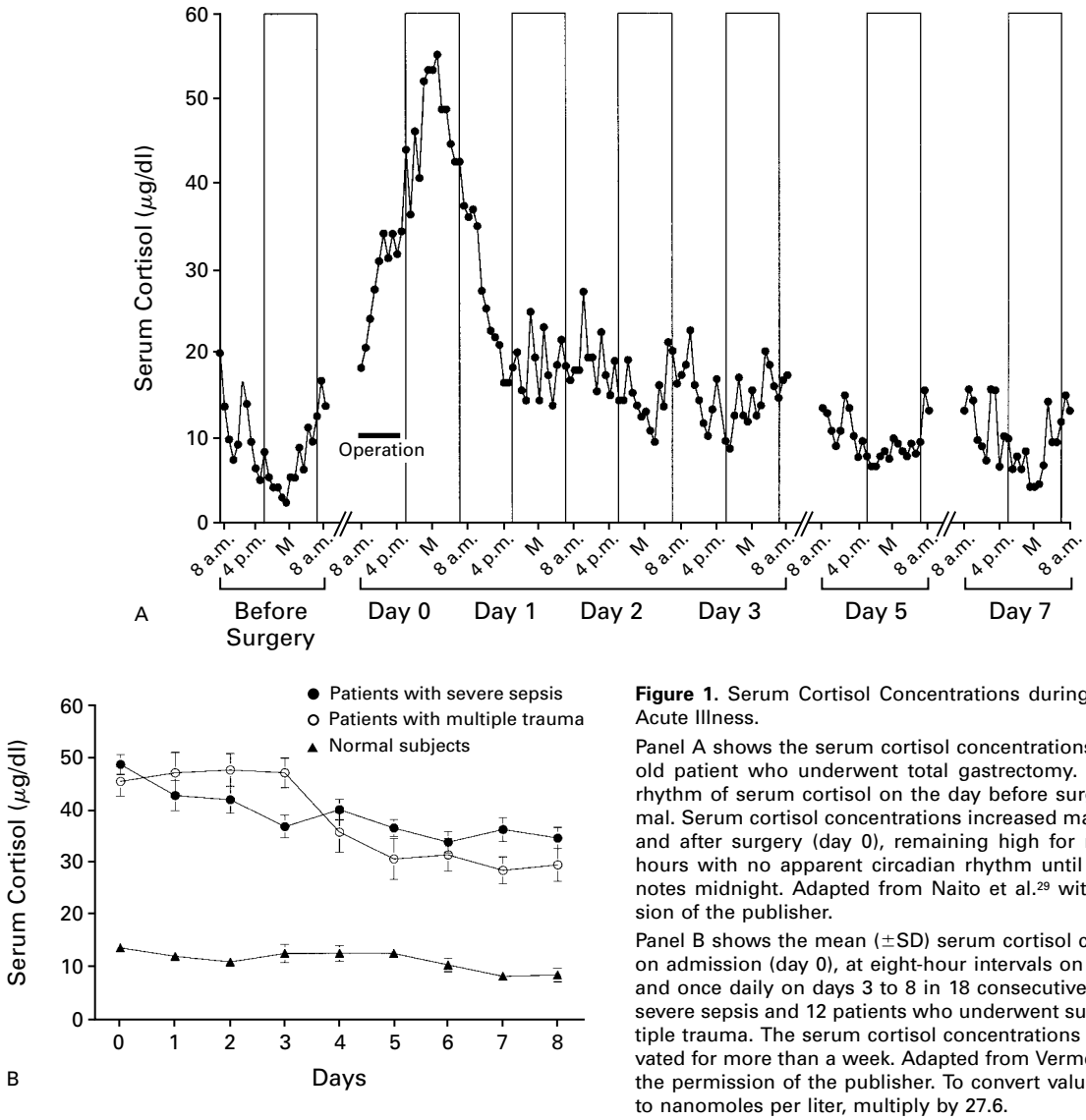

Figure 1. Serum Cortisol Concentrations during Surgery and Acute Illness.

Panel A shows the serum cortisol concentrations in a 70-year-old patient who underwent total gastrectomy. The circadian rhythm of serum cortisol on the day before surgery was normal. Serum cortisol concentrations increased markedly during and after surgery (day 0), remaining high for more than 72 hours with no apparent circadian rhythm until day 7. M denotes midnight. Adapted from Naito et al.[29] with the permission of the publisher.

Panel B shows the mean (±SD) serum cortisol concentrations on admission (day 0), at eight-hour intervals on days 1 and 2, and once daily on days 3 to 8 in 18 consecutive patients with severe sepsis and 12 patients who underwent surgery for multiple trauma. The serum cortisol concentrations remained elevated for more than a week. Adapted from Vermes et al.[30] with the permission of the publisher. To convert values for cortisol to nanomoles per liter, multiply by 27.6.

rum cortisol concentrations that are regarded as normal in normal subjects may be inappropriately low in patients who are severely ill, suggesting the existence of relative adrenal insufficiency. For example, a cortisol concentration of less than 10 μg per deciliter (276 nmol per liter) in a random serum sample has been proposed as abnormal during acute illness[37] and, conversely, serum cortisol concentrations above 18 μg per deciliter (497 nmol per liter) after corticotropin stimulation as indicating adequate adrenal reserve.

Several patterns of response in critically ill patients can be recognized. In most patients, serum cortisol concentrations increase to levels above 18 μg per deciliter after the administration of corticotropin,[38-40] but in those with high base-line serum cortisol concentrations, the increment after corticotropin administration may be small, a finding that might have a predictive value with regard to mortality.[5] Among 32 patients with septic shock, all but 1 of whom had basal serum cortisol concentrations above 11 μg per deciliter (303 nmol per liter), all 13 who had a poor response to corticotropin (increase in serum cortisol, less than 9 μg per deciliter [248 nmol per liter]) died. In contrast, only 6 of the 19 patients who had an increase in serum cortisol of more than 9 μg per deciliter died.[41] In another study, 5 of 26 patients with sepsis had subnormal responses; only 1 of the 5 patients survived, and this patient was treated with corticosteroids.[25] On the other hand, the failure of the rapid corticotropin test to reveal corticotropin deficiency demonstrable by insulin tolerance[42,43] or metyrapone testing[44,45] means that it cannot be fully relied on, especially in patients with hypothalamic or pituitary disease.[46]

The relative lack of a serum cortisol response to

corticotropin in some critically ill patients may be due to the fact that the normal hypothalamic–pituitary–adrenal axis is already maximally stimulated, but it may also be due to interference with the corticosteroid-synthesizing capacity of the adrenal cortex (for example, by adrenal hemorrhage, adrenal metastases, or drugs; see below and Table 1). Support for a contributory role of limited adrenocortical reserve in the deterioration of critically ill patients comes from a study showing that, of 133 consecutive patients in an intensive care unit whose morning serum cortisol concentrations progressively fell to less than 11.8 μg per deciliter (326 nmol per liter), 27 percent died.[48]

In recent years there have been reports of a number of critically ill patients with relative adrenal insufficiency.[49,50] Virtually all these patients had complicated multiorgan disease, high cardiac output, low peripheral vascular resistance, shock, and normal serum cortisol concentrations, findings that rule out primary adrenal insufficiency. In these patients, administration of hydrocortisone (100 to 300 mg per 24 hours) diminished or eliminated the requirement for vasopressor drugs, supporting the concept of occult relative adrenal insufficiency.[10,11]

Evidence of the important role of intact hypothalamic–pituitary–adrenal function in the survival of critically ill patients with multiple trauma and the role of occult relative adrenal insufficiency comes from the intensive care unit of the University Hospital of Glasgow, Scotland.[51] Between 1969 and 1980, the mortality rate among patients with multiple injuries varied between 22 and 29 percent. In 1981 and 1982, mortality rose to 44 percent, despite the absence of change in the injury-severity score of the patients at the time of admission. This increase in mortality coincided with the introduction of a short-acting hypnotic drug, etomidate, given to optimize respiratory assistance. This drug was subsequently found to be a selective inhibitor of adrenal 11β-hydroxylase, the enzyme that converts deoxycortisol to cortisol.[52]

As shown in Figure 2, administration of etomidate during an elective short surgical procedure was accompanied by a subnormal increase in serum cortisol concentrations, despite an increase in corticotropin and deoxycortisol secretion. The clinical outcome of the minor surgical procedure was not altered in these patients. However, in patients with multiple injuries (including those with hypovolemia, infections, and organ failure), etomidate-induced partial adrenocortical insufficiency seemed to be the additional factor that changed the course of the illness, nearly doubling mortality.[51,53] These findings indicate that even slight impairment of the adrenal response during severe illness can be lethal, and they support the concept that the apparently poor serum cortisol responses to corticotropin and the decline in morning serum cortisol concentrations in these patients may be causes, rather than consequences, of the severe illness.

TABLE 1. FACTORS CONTRIBUTING TO THE DEVELOPMENT OF RELATIVE HYPOADRENALISM IN CRITICALLY ILL PATIENTS.

Partial destruction of the adrenal cortex
Preexisting or previously undiagnosed asymptomatic diseases of the adrenal glands
Autoimmune adrenalitis
Tuberculosis
Metastases
Acute partial destruction of the adrenal glands
Hemorrhage
Massive retroperitoneal bleeding
Thrombocytopenia
Anticoagulant therapy
Bacterial (meningococcemia), viral, or fungal infections
Previously unknown hypothalamic–pituitary disease resulting in undiagnosed secondary hypothalamic–pituitary–adrenal insufficiency
Cytokine-mediated inhibition of corticotropin release during septic shock?[47]
Drug-related factors
Previously unknown corticosteroid therapy
Medroxyprogesterone, megestrol acetate
Increased metabolism of cortisol: phenytoin, phenobarbital, rifampin
Changes in cortisol synthesis: ketoconazole, etomidate, aminoglutethimide, metyrapone, mitotane, trilostane
Interference with corticotropin action: suramin
Peripheral glucocorticoid-receptor blockade: mifepristone

The incidence of acute (total) adrenal insufficiency after routine surgery is low, ranging from 0.01 to 0.7 percent in more than 70,000 patients.[54-56] Total adrenal insufficiency is also rare in severely ill patients, occurring in 2 to 3 percent of patients.[3,5,57] However, the notion of total adrenal insufficiency has been gradually replaced by the concept of occult or relative adrenal insufficiency, caused by preexisting disease, concomitant factors, or complications that only partially reduce the adrenocortical capacity to produce cortisol (Table 1). This relative adrenal insufficiency might contribute to a fatal outcome, especially in patients with multiorgan failure.[25,58]

Symptoms and signs that might raise suspicion of the existence of relative adrenal insufficiency are shown in Table 2. Inappropriately low serum cortisol concentrations or impaired serum cortisol responses to corticotropin also suggest the presence of relative adrenal insufficiency. It is important to recognize this condition, because therapy with corticosteroids can improve the clinical condition of these patients, making their outcome dependent only on the underlying disease.

In conclusion, the practical use of the corticotropin test in severely ill patients is at present limited to the diagnosis of total adrenal insufficiency, and in exceptional cases the diagnosis of secondary adrenal insufficiency is missed. No strict biochemical criteria for relative adrenal insufficiency are currently avail-

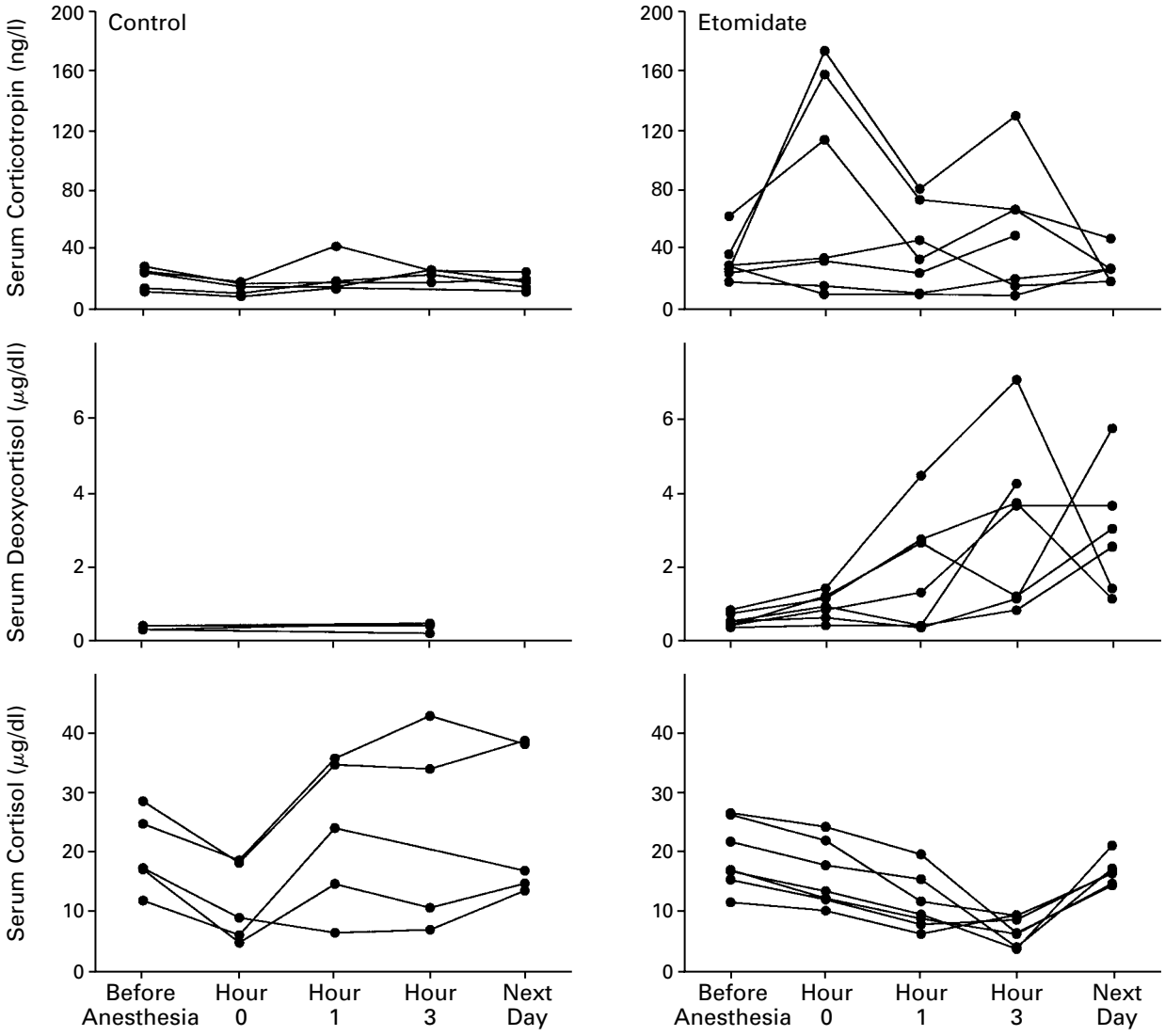

Figure 2. Effect of Anesthesia with Thiopental, Pancuronium, and Fentanyl (Control, Five Patients) and with Etomidate (Seven Patients) in Patients Undergoing Peroral Endoscopy and Microlaryngeal (Laser) Surgery of the Larynx.

The course of surgery and anesthesia (hour 0) and the outcome (up to 24 hours) were similar in both groups of patients, with no subjective reports of symptoms and no differences in blood pressure. Note the inhibition of 11β-hydroxylation of the adrenal cortex by etomidate, as evidenced by increased serum corticotropin and 11-deoxycortisol concentrations and lowered serum cortisol concentrations. Adapted from de Jong et al.[52] with the permission of the publisher. To convert values for cortisol to nanomoles per liter, multiply by 27.6; to convert values for deoxycortisol to nanomoles per liter, multiply by 28.9; to convert values for corticotropin to picomoles per liter, multiply by 0.22.

able. This diagnosis should be suspected, however, when administration of hydrocortisone to severely ill patients is followed by a period of diminished or no need for vasopressor drugs.

CORTICOSTEROID THERAPY FOR CRITICAL ILLNESS

The value of high-dose corticosteroid therapy in critically ill patients with an intact hypothalamic–pituitary–adrenal axis is controversial. Most clinical studies have been carried out in patients with sepsis, often complicated by shock and multiorgan failure.[59] In two meta-analyses of the effect of corticosteroids in patients with sepsis or septic shock,[60,61] only 9 of 49 and 10 of 124 studies were considered of sufficient methodologic quality to be included. Overall, there was no beneficial effect of corticosteroids on survival in patients with sepsis or septic shock.[60,61]

However, some circumstances and conditions in which corticosteroid administration might have been beneficial should be mentioned.

First, in some studies, administration of corticosteroids was beneficial only during the first few hours after the onset of shock.[59] The meta-analyses did not address this aspect of the therapy because of lack of information in the published trials about the time of administration of corticosteroids. Nonetheless, delays in administering corticosteroids could explain in part the lack of benefit of corticosteroid therapy with respect to outcome in patients with septic shock.

Second, in the two clinical trials with the best methodologic-quality scores,[59,62] patients with gram-negative sepsis responded better to corticosteroid treatment than did patients with other infections. However, the slight advantage for the patients with gram-negative sepsis was outweighed by a higher mortality among the corticosteroid-treated patients with sepsis that was caused by gram-positive organisms.

It is therefore possible that very early initiation of treatment or even prophylactic therapy with corticosteroids in patients at risk for gram-negative infections might be effective in reducing the generalized inflammatory response to those infections. Corticosteroids were also beneficial in randomized trials in patients with bacterial meningitis,[63] typhoid fever,[64] acute spinal cord injury,[65] *Pneumocystis carinii* pneumonia,[66] and the adult respiratory distress syndrome.[67]

Another shortcoming of the meta-analyses of studies of corticosteroids in patients with sepsis or septic shock is the lack of information about patients with underlying adrenocortical disease or relative adrenocortical insufficiency. Such patients benefit from corticosteroid treatment, but they are lost in the overall analysis. Genetically based variations among normal subjects in the threshold level of corticosteroid responses to stress could also affect the subjects' survival when given corticosteroid therapy.[68,69]

CORTICOSTEROID THERAPY IN PATIENTS WITH KNOWN ADRENAL DYSFUNCTION

Hypothalamic–pituitary–adrenal activation during surgery and severe illness is even more complicated in patients receiving corticosteroid therapy than in patients presumed to have previously normal adrenal function. Patients receiving corticosteroid therapy can be divided into two categories. One category consists of patients with chronic autoimmune or inflammatory diseases (such as asthma, ulcerative colitis, rheumatoid arthritis, or skin disease) who are being treated or have recently been treated with high doses of corticosteroids. The second category consists of patients receiving cortisol-replacement therapy because of hypothalamic–pituitary–adrenal hypofunction, whether of the hypothalamus (for example, from previous irradiation), the pituitary (for example, from adenomas), or the adrenals (for example, from Addison's disease).

TABLE 2. SYMPTOMS AND SIGNS THAT RAISE THE SUSPICION OF HYPOADRENALISM IN CRITICALLY ILL PATIENTS.

Unexplained circulatory instability
Discrepancy between the anticipated severity of the disease and the present state of the patient, including nausea, vomiting, orthostatic hypotension, dehydration, abdominal or flank pain (indicating acute adrenal hemorrhage), fatigue, and weight loss
High fever without apparent cause (negative cultures), not responding to antibiotic therapy
Unexplained mental changes: apathy or depression without a specific psychiatric disturbance
Vitiligo, altered pigmentation, loss of axillary or pubic hair, hypothyroidism, hypogonadism
Hypoglycemia, hyponatremia, hyperkalemia, neutropenia, eosinophilia

Patients with Chronic Autoimmune or Inflammatory Diseases Treated with Corticosteroids

The duration of corticosteroid therapy, the highest dose, and the total cumulative dose have long been considered important predictors of the suppression of hypothalamic–pituitary–adrenal function.[70-74] However, high-dose corticosteroid therapy and prolonged treatment do not invariably correlate with the degree and duration of hypothalamic–pituitary–adrenal suppression,[72,73,75,76] and the time to recovery after discontinuation of corticosteroid therapy is highly variable. It can be as short as two to five days[76] or as long as nine months to one year.[70,71] Therefore, it is hard to predict, on the basis of the history of corticosteroid therapy, which patient will have hypothalamic–pituitary–adrenal deficiency when therapy is discontinued, even if the patient was taking a single daily dose or alternate-day doses.[77,78]

An important question is how well a test of hypothalamic–pituitary–adrenal function predicts the responses of the cardiovascular system and of other systems to acute stress in a patient who has been treated with corticosteroids. In an early study of several tests (insulin-induced hypoglycemia, metyrapone, lysine vasopressin, and corticotropin) and the subsequent response to surgery in a group of corticosteroid-treated patients,[73,79] more patients had subnormal serum cortisol responses to insulin and metyrapone than to the other tests, but the best indicator of the maximal serum cortisol concentration during surgery was the peak serum cortisol concentration after the administration of corticotropin.[73,79,80]

The most important measure of the value of any test of hypothalamic–pituitary–adrenal function, however, is its ability to predict the clinical response of a patient to the stress of surgery or acute illness. When blood pressure during and after surgery is taken as

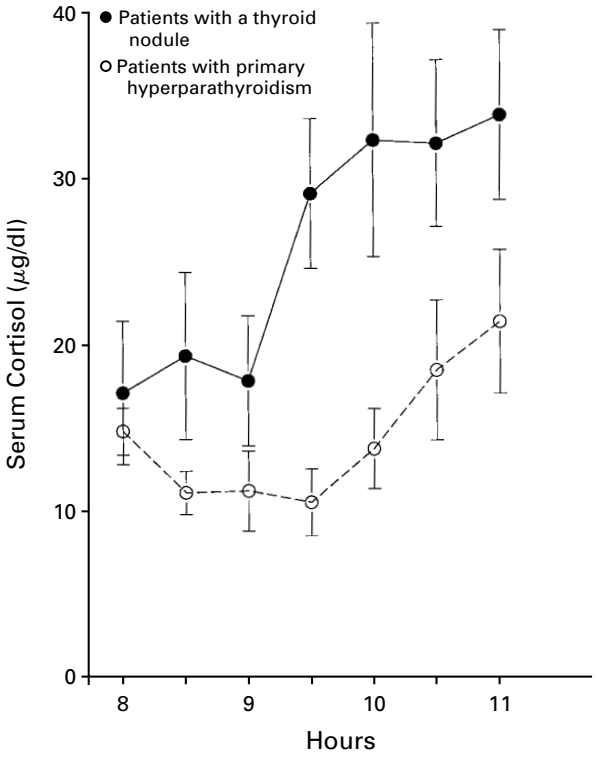

Figure 3. Effect of Anesthesia and Neck Exploration on Mean (±SE) Serum Cortisol Concentrations in Seven Control Patients with a Thyroid Nodule and Six Patients with Primary Hyperparathyroidism Treated for 10 Days with 30 mg of Prednisone Daily up to 3 Days before Operation.

During identical routine anesthesia and a similar surgical procedure, as well as during the subsequent 24 hours, there were no differences in subjective reports of symptoms or blood pressure between the two groups. Adapted from Janssens[89] with the permission of the publisher. To convert values for cortisol to nanomoles per liter, multiply by 27.6.

the end point, neither basal nor corticotropin-stimulated serum cortisol concentrations predict changes in blood pressure in corticosteroid-treated patients undergoing surgical stress without corticosteroid supplementation.[40,73,79]

A number of case histories and more extensive studies of corticosteroid-treated patients[5,9-11,25,40,81-83] describe the catastrophic effects of hypocortisolism during surgery and the dramatic beneficial effects of corticosteroid therapy. In retrospect, however, many confounding factors were present that make the interpretation of these reports difficult. These factors include interfering diseases, complications of surgery or anesthesia, the use of drugs acting directly or indirectly on adrenal function (Table 1), and the development of the corticosteroid-withdrawal syndrome in patients who suddenly stop long-term therapy with high-dose corticosteroids,[84] with symptoms and signs similar to those of acute adrenal insufficiency (anorexia, nausea, vomiting, weight loss, and depression).

Recent studies indicate that the daily rate of cortisol production in normal subjects is lower than previously thought (5.7 mg [15.7 μmol] per square meter of body-surface area per day), as opposed to 12 to 15 mg (33 to 41 μmol) per square meter per day.[85] This lower rate of cortisol production corresponds to about 10 to 12 mg of oral hydrocortisone equivalent per square meter per day, because of incomplete bioavailability resulting from first-pass hepatic metabolism of oral hydrocortisone. In adults the adrenal glands produce about 50 mg (138 μmol) of cortisol per 24 hours during minor surgical procedures and 75 to 150 mg (207 to 414 μmol) per 24 hours during major surgery[40]; cortisol secretion in the first 24 hours after surgery seldom exceeds 200 to 300 mg (552 to 828 μmol),[9,40] suggesting that in critically ill patients those are the maximal doses of hydrocortisone that should be administered, preferably as a continuous intravenous infusion. The reasons for withholding higher doses include the catabolic effects of high doses on muscle and wound healing, the anti-insulin effects on glucose metabolism, and the antiinflammatory effects that may allow infections to worsen.[9]

In several recent studies of corticosteroid-treated patients undergoing surgery while receiving their previous doses, no patient had any intraoperative or postoperative hypotension or other problems of any kind.[86-88] Studies in adrenalectomized monkeys also support the concept that a replacement dose of hydrocortisone is enough to maintain normal cardiac contractility and vascular tone during the stress of a short, uncomplicated surgical procedure.[18] However, the doses of hydrocortisone given to these monkeys during surgery might have been rather high (32 mg [88 μmol] per square meter per day).

Larger doses of corticosteroids can blunt the endogenous hypothalamic–pituitary–adrenal response to surgery but are not associated with any clinical or metabolic abnormalities. For example, the serum cortisol concentrations during exploratory neck surgery were lower in patients given 30 mg of prednisone for 10 days preoperatively than in untreated patients (Fig. 3), but none had any intraoperative or postoperative problems.[89]

These results have led to the suggestion that for elective surgery and most acute illnesses, continuation of the current dose of corticosteroids suffices to maintain cardiovascular function.[86-88] However, if the operation or acute illness is complicated or prolonged, especially in the presence of the factors listed in Table 1, higher doses of corticosteroids should be administered, by doubling or tripling the current oral dose or by giving hydrocortisone intravenously at a dose of 100 to 150 mg daily.

The approach of increasing the dose of corticosteroids only in patients with complications or prolonged illness, however, has practical risks. Although

most patients treated with 5 to 15 mg of prednisone daily, for example, may respond normally, even to severe stress,[9,86,87] some may not, and if supplemental corticosteroid is not given, physicians must remain alert to the possibility of unexpected complications for which additional corticosteroid might be beneficial. Overtreatment for a day or two is unlikely to cause any harm.

A consensus paper[9] makes reasonable and clear recommendations for the dose and duration of corticosteroid supplementation according to both the previous dose and the severity of the surgical stress and illness. For minor stress, a total dose of 25 mg is recommended; for moderate stress, 50 to 75 mg; and for major stress, 100 to 150 mg of hydrocortisone or its equivalent should be given for one to three days.[9] A special group of patients consists of those who receive corticosteroids topically (by inhalation, intranasally, transdermally, or by enema). Hypothalamic–pituitary–adrenal suppression is very rare in these patients,[5,40] and it seems safe to withhold additional corticosteroid during minor or moderate surgical procedures or illnesses in these patients, as long as their clinical course is uncomplicated.

Patients with Previously Diagnosed Hypothalamic–Pituitary–Adrenal Insufficiency

Few, if any, patients receiving hydrocortisone-replacement therapy for corticotropin or cortisol deficiency have an increase in serum cortisol concentrations during surgery, trauma, infections, or other severe illnesses. All these patients should be given supplemental corticosteroid therapy in the form of 100 to 150 mg of hydrocortisone by continuous intravenous infusion during any severe illness or surgery. Patients who travel frequently should wear a bracelet with multilingual information concerning their corticosteroid dependence.

CONCLUSIONS

During critical illness, the hypothalamic–pituitary–adrenal axis is activated, as demonstrated by increased serum corticotropin and cortisol concentrations. In most patients with adrenal insufficiency, determination of the response of the serum cortisol concentration to corticotropin is helpful in making the diagnosis. However, occult relative adrenal insufficiency, defined as a state in which corticosteroid administration diminishes or eliminates the requirement for vasopressor drugs, rather than as a state in which hypothalamic–pituitary–adrenal function is clearly abnormal, may occur in some critically ill patients. Patients receiving treatment with corticosteroids for chronic autoimmune or inflammatory diseases need less additional corticosteroid during severe illness and perioperatively than those receiving replacement therapy for hypothalamic–pituitary–adrenal insufficiency.

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