Assessment of Adrenocortical Function in the Critically Ill

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ABSTRACT

Objective: *To review current concepts in the diagnosis of adrenocortical disease in the critically ill patient.*

Data sources: *A review of articles reported on adrenocortical insufficiency in the acutely ill patient.*

Summary of review: *The contribution of adrenal insufficiency to the morbidity of critically ill patients is currently under renewed scrutiny. The debate continues about the role of steroids in sepsis and essentially the question remains unanswered. Central to this debate is the issue of whether adrenal insufficiency is common in the critically ill patient. What is incontrovertible is that adrenocortical function is essential for host survival during critical illness, but what constitutes adrenocortical insufficiency in critically ill patients is not clear.*

Absolute adrenocortical insufficiency (diagnosed by very low plasma cortisol concentrations) is uncommon in the intensive care population. The diagnosis of relative adrenocortical insufficiency (elevated basal plasma cortisol with a subnormal increase in plasma concentrations following an ACTH stimulus) continues to generate debate. The controversy surrounding the role of steroids in sepsis and the confusion over the criteria for diagnosing adrenal insufficiency in the critically ill are reviewed.

Conclusions: *We suggest that the following caveats be borne in mind when diagnosing adrenal insufficiency in the critically ill patient. Firstly, the gold standard for the diagnosis has not been established. Secondly, caution must be exercised when interpreting a single plasma cortisol value. In the event of a single result indicating adrenal hypofunction, we suggest repeating the measurements after a 6 to 12 hour interval. The clinician must also be aware of variations in cortisol concentrations induced by the assay. Thirdly, the clinician must be aware of the potential limitations of the conventional high dose corticotrophin test. We also suggest that plasma free cortisol is more relevant than total plasma cortisol in the assessment of adrenal function in critical illness and that the low dose corticotrophin test is more sensitive than the conventional high dose test. These areas should be the subject of further investigations.*
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Key words: Adrenocortical failure, adrenocortical function, critically ill, corticosteroid, cortisone

In undertaking the care of critically ill patients, we look after individuals who are often stretched to physiological extremes. They are exposed to a wide variety of insults whose effect under normal circumstances is to initiate a complex neuroendocrine pathway, the so-called "stress response". It is becoming clearer that the magnitude of this response in critically ill patients is of prime importance, and can provide valuable information as to outcome. What is less clear is what constitutes an appropriate response under conditions of extreme stress, and whether artificial stimulation of a 'less than appropriate response' is beneficial. In this context, the contribution of adrenal insufficiency to the morbidity of critically ill patients is currently under

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renewed scrutiny.

Adrenal insufficiency is considered to be a frequent problem in septic patients,[1] and there is evidence that steroid replacement therapy in this group may improve outcome.[2] Consequently, recognition of adrenal insufficiency in critical illness has assumed considerable importance in recent years. In this article we explore the controversial history surrounding the use of corticosteroid therapy in sepsis and septic shock which provides the basis for a critical evaluation of the difficulties involved in the interpretation of the various biochemical tests of adrenal function in critically ill patients. Plasma cortisol levels are reported in both μg/dL and nmol/L (1 μg/dL = 27.6 nmol/L).

THE ADRENAL CORTEX

The adrenal glands are functionally divided into medulla and cortex and are responsible for the secretion of four major classes of hormones; catecholamines, sex hormones, mineralocorticoids and glucocorticoids. The major glucocorticoid synthesised by the adrenal cortex is cortisol which plays a pivotal role in normal metabolism. It is also necessary for the synthesis of adrenergic receptors, normal immune function, wound healing and vascular tone.

Cortisol secretion is under the control of the hypothalamic pituitary axis. There are a variety of stimuli to secretion, including stress, tissue damage, cytokine release, hypoxia, hypotension and hypoglycaemia. These factors act upon the hypothalamus to favour the release of corticotrophin releasing hormone (CRH) and vasopressin. Corticotropin releasing hormone is synthesised in the hypothalamus and carried to the anterior pituitary in portal blood, to stimulate the anterior pituitary to secrete adrenocorticotropic hormone (ACTH), which in turn stimulates the release of cortisol, mineralocorticoids (principally aldosterone) and androgens from the adrenal cortex. Corticotropin releasing hormone is the major (but not the only) regulator of ACTH release and is secreted in response to a normal hypothalamic circadian regulation and various forms of 'stress'. Vasopressin, oxytocin, angiotensin II and beta-adrenergic agents also stimulate ACTH release while somatostatin, beta-endorphin and enkephalin decrease ACTH release. ACTH has a half-life of 10 - 15 minutes. Both ACTH and cortisol are secreted in a cyclical fashion throughout the 24 hour period. Cortisol has a negative feedback on the hypothalamus and pituitary, inhibiting hypothalamic CRH release induced by stress, and pituitary ACTH release induced by CRH.

Under normal circumstances, cortisol is secreted in pulses and in a diurnal pattern.[3] The normal daily output of cortisol is 40 - 80 μmol/day (i.e. 15 - 30 mg/day), producing a maximum plasma cortisol level of 110 - 520 nmol/L (4 - 19 μg/dL) at 8 - 9 a.m., and a minimal cortisol level of < 140 nmol/L (< 5 μg/dL) after midnight.

Cortisol exists in plasma in bound form, bound to an alpha-globulin called transcortin (corticosteroid-binding globulin or CBG) and albumin and in a free form. The free hormone is the active form. At normal levels of total plasma cortisol (e.g. 375 nmol/L or 13.5 μg/dL) less than 5% exists as free cortisol in the plasma. Cortisol binding by CBG in normal subjects can bind approximately 700 nmol/L (i.e., 25 μg/dL). At levels greater than this, the increase in plasma cortisol is largely in the unbound fraction. Corticosteroid-binding globulin is a substrate for elastase, a polymorphonuclear enzyme that cleaves CBG, markedly decreasing its affinity for cortisol.[4] This enzymatic cleavage results in the liberation of free cortisol, the biologically active hormone, at sites of inflammation.

During periods of stress, trauma or infection, there is an increase in CRH and ACTH secretion and a reduction in the negative feedback effect, resulting increased in cortisol levels, in amounts roughly proportional to the severity of the illness.[5,6] Cortisol promotes muscle protein catabolism and stimulates gluconeogenesis to produce glucose from the amino acids provided by protein catabolism, it also promotes the lipolytic effect of catecholamines. Cortisol enhances vascular smooth muscle and myocardium responsiveness to noradrenaline or adrenaline and renal water excretion, all of which are impaired in the absence of glucocorticoids. The half-life of cortisol is 60 - 90 minutes.

In pharmacological doses, glucocorticoids have anti-inflammatory and immunosuppressive effects, causing a reduction in the peripheral lymphocyte, eosinophil and monocyte count, and an increase in neutrophil count.[7] The relative potencies of the commonly used glucocorticoids are listed in Table 1.

Hydrocortisone is the synthetic equivalent of cortisol and is assigned the glucocorticoid and mineralocorticoid equivalent of 1 (one). Prednisone and prednisolone are equivalent, as are triamcinolone and methylprednisolone, and betamethasone and dexamethasone.[8]

The steroid odyssey

The syndrome of hypoadrenalism was first described by Thomas Addison in 1849.[9] It was more than a century later that the first clinical use of corticosteroids was published by Philip Hench.[10] The first report of the use of corticosteroids in sepsis was published in 1951 by Hahn *et al*,[11] in a cohort of patients with streptococcal infections where they documented a reduction in the incidence of post streptococcal complications with the use of cortisone. Subsequent studies on the use of corticosteroids in sepsis and typhoid also confirmed its

Table 1 Characteristics of the commonly used glucocorticoids

Agent	Dose (mg)	Mineralocort-icoid potency	Glucocort-icoid potency	duration of action (hr)	Plasma half life (min)
Cortisone	25	1	0.8	8	90
Hydrocortisone	20	1	1	8	90
Prednisolone	5	0.8	4	24	150
Methylprednisolone	4	0.5	5	24	150
Dexamethasone	0.75	0	25	36	250

beneficial role in these conditions.[12,13]

Over the next few years, the emphasis shifted from one of "steroid success" to "steroid excess" with proponents using up to 30 mg/Kg methylprednisolone in severe sepsis.[14,15] The results from these studies either did not demonstrate any benefit or showed excess mortality with its use. Consequently, there was a waning in the enthusiasm for the use of corticosteroids in patients with sepsis.

However, the pendulum appears to have swung back with the publication of two studies, one in patients with meningitis[16] and the other in patients with septic shock,[2] although evidence from three meta-analyses have not supported the routine use of steroids in critically ill patients with sepsis.[17-19] Thus, the debate continues about the role of steroids in sepsis and essentially the question remains unanswered.

ADRENAL INSUFFICIENCY IN THE CRITICALLY ILL

Central to this debate is the issue of whether there is, or is not, adrenal insufficiency in the critically ill patient. What is incontrovertible is that adrenocortical function is essential for host survival during critical illness, but what constitutes adrenocortical insufficiency in the critically ill patient is not clear.

Absolute adrenocortical insufficiency (diagnosed by very low plasma cortisol concentrations) is uncommon in the intensive care population. The diagnosis of relative adrenocortical insufficiency (i.e. elevated basal plasma cortisol levels with a subnormal increase in plasma concentrations following an ACTH stimulus) continues to generate much debate.[20] Despite many publications on this subject over the last 5 decades, this subject continues to be dogged by controversy.

Assessment of adrenal function

Changes in plasma electrolyte concentrations and blood eosinophilia as markers of adrenal hypofunction lack sensitivity and specificity.[20] Consequently, the evaluation of adrenal function in critical illness relies largely on biochemical assessment of the adrenal cortex. These tests comprise either basal hormone assays or dynamic function tests as summarised in Table 2.

In routine intensive care practice, generally only the plasma cortisol or cosyntropin test are used. However, translating the results of these investigations from the normal patient population to the critically ill is problematic, and has lead to a number of controversies.

Table 2. Biochemical tests for screening for adrenal dysfunction

Plasma Cortisol
Urine Cortisol
Plasma ACTH
ACTH Stimulation test (Cosyntropin test)
Metapyrone test
Insulin hypoglycaemia test
CRH stimulation test

What are the sources of confusion regarding diagnostic testing?

Plasma cortisol

a) *What constitutes an appropriate baseline cortisol in the stressed critically ill patient?*

An elevated total plasma cortisol in stressed ICU patients has been demonstrated in a number of studies. The maximum stress-induced output of cortisol is thought to be up to 555 μmol/day (i.e., 200 mg/day), with corresponding plasma levels of approximately 1650 nmol/L (i.e., 60 μg/dL).[1]

In Figure 1 a summary of mean plasma cortisol measurements from controls in 4 studies[3,21-23] and in critically ill patients in 8 studies,[1,24-30] is presented.

It is clear that critically ill patients have a higher plasma cortisol (e.g. 460-1400 nmol/L) than healthy volunteers. However, given the wide ranges seen in these patients it is difficult to determine what constitutes a normal reference range for the critically ill patient. Compounding this difficulty is the fact that the levels vary depending on the stress level and the underlying diagnosis. This is reflected in the fact that studies have reported a wide range of incidence

of adrenal insufficiency in the critically ill (e.g. 1.5% to 75%) although data from several studies appear to suggest that a threshold value of 414 nmol/L may best identify patients with corticosteroid insufficiency.[27,28]

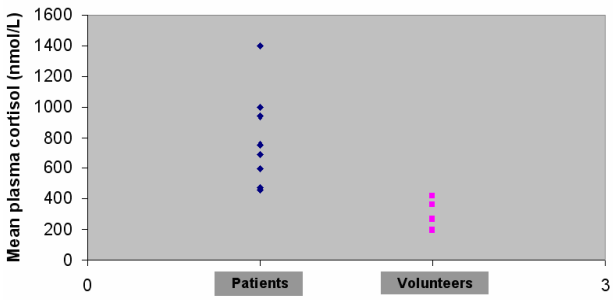

Figure 1. Distribution of mean plasma cortisol in critically ill patients compared with healthy volunteers.

b) *Lack of a clear relationship between serum cortisol levels and outcome*

Annane *et al*,[39] published a graded outcome prediction scale based on baseline cortisol and the cortisol response to cosyntropin in critically ill septic patients.. However, a clear relationship between serum cortisol and mortality in critical illness has not been demonstrable (Figure 2).[26,27,31-39]

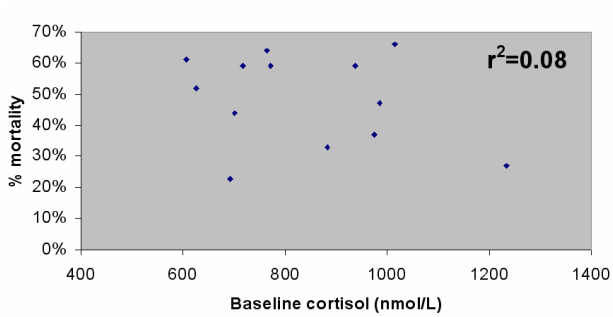

Figure 2. Pooled data demonstrating the relationship between baseline plasma cortisol and mortality in critically ill patients.

c) *Variations in cortisol assay*

Confusion occurs due to variations in the accuracy and precision of plasma cortisol assays. The coefficient of variations of cortisol estimations is usually 10 - 12%, and the same specimen submitted to different assays can yield significantly different results.[40] Therefore, reference ranges established at one institution may not be applicable to another.

d) *Impact of circadian rhythm*

Finally, it has not been established whether a random cortisol adequately reflects the 24-hour secretory profile in the critically ill patient. The pronounced diurnal cycle of cortisol secretion seen in health[41] may be disrupted in the intensive care unit due to factors such as pain, light, sound and sleep interruption.[42] This may interfere with cortisol secretory patterns. Assessment of cortisol secretion under these conditions would require sequential evaluation over a prolonged period to determine optimal time periods for sampling. The biological half life of cortisol is 90 minutes. Any sampling interval longer than this may potentially miss significant peaks and troughs. Data from our study reveal the presence of significant fluctuations in plasma cortisol levels measured over a 24 hour period and indicate that a diagnosis of impaired cortisol secretion may be erroneous if based on a single plasma cortisol measurement.

Cosyntropin test

This investigation forms the cornerstone of adrenal function assessment in the intensive care unit. It is performed by measurement of a baseline serum cortisol level followed by parenteral administration of 250µg of synthetic ACTH. Further serum cortisol levels are obtained thereafter at 30 and 60 minutes. The normal response is quoted as a rise in serum cortisol levels to above 500 - 550 nmol/L or an increase of greater than 250 nmol/L. However, these values have been obtained from studies in unstressed volunteers, so their applicability in the setting of critical illness is not clear. Observational studies demonstrated that patients with a high baseline cortisol level who had a reduced response to the cosyntropin test (e.g. < 250nmol/L or 9 ug/dL) had a higher mortality.[1] However, pooled data from other studies would suggest that the threshold response is close to 400 nmol/L (Figure 3).[26,27,31-39]

Critics have pointed out that the test is only a measurement of adrenal reserve, not adrenal function, and thus its use to determine adrenal insufficiency in the setting of sepsis is inappropriate. A normal response to the test does not rule out adrenal suppression as the dose of ACTH used is far higher than normal physiological concentrations and may override adrenal resistance to corticotrophin, thus producing a false negative test in patients who have mild secondary adrenal insufficiency. This has led to the suggestion that a "low dose" cosyntropin test, utilising only 1µg of corticotropin, would be more physiological and result in concentrations similar to that seen in the insulin hypoglycemia and the metyrapone tests.[43] To date there are scant data on the use of this test in critically ill patients.

Plasma free cortisol

While the majority of circulating cortisol (e.g. 90%) is bound to CBG, it is only the free fraction that possesses biological activity. During critical illness,

levels of cortisol binding globulin decrease,[5] and free cortisol levels may increase secondary to the cleavage of cortisol binding globulin by neutrophil elastase. However, commercial assays only measure the total plasma cortisol, so a physiologically significant rise in free cortisol can be missed.

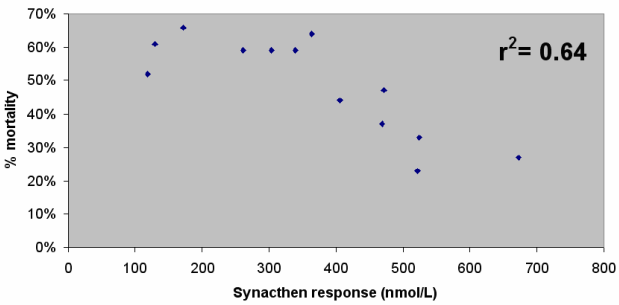

Figure 3. Pooled data demonstrating the relationship between plasma cortisol response to cosyntropin (synacthen) and mortality in critically ill patients.

Urine cortisol reflects free plasma levels so that raised urine free cortisol suggest elevated plasma free cortisol a result which we found in septic patients[24] Our group also confirmed this phenomenon in salivary cortisol measurements (which predominantly reflects the free cortisol fraction) in critically ill patients.[44]

Free cortisol levels in intensive care patients have been examined in a recent study[45] which demonstrated that while serum total cortisol levels were reduced in hypoproteinaemic patients, the serum free cortisol levels were elevated. The authors suggested that a baseline free cortisol level of 55.2 nmol/L (2.0 µg/dL) should be considered the threshold level that identifies patients at risk for adrenal insufficiency during critical illness and that the corticotropin-stimulated serum free cortisol concentration of 85.3 nmol/L (3.1 µg/dL), or greater, defines a normal response in critically ill patients.

Plasma ACTH levels

Full assessment of the integrity of the hypothalamus-pituitary-adrenal (HPA) axis requires the concomitant measurement of plasma ACTH and cortisol concentrations. The normal plasma ACTH concentrations range from 10 - 50 ng/L. Primary hypoadrenal states are characterised by low plasma cortisol and high ACTH levels, whilst secondary hypoadrenalism is typified by both low plasma cortisol and ACTH concentrations. There are few studies examining plasma ACTH in critically ill patients. In view of the paucity of data, no diagnostic criteria have been developed based on plasma ACTH concentrations to diagnose adrenal insufficiency in the critically ill patient.

Plasma ACTH has a half life of 10 minutes and this, combined with the technical difficulties in processing specimens for an accurate ACTH assay, has meant that this investigation has not received much attention in the critically ill patient.

Miscellaneous

Other factors contributing to the confusion in this area are the issues of tissue specific resistance to cortisol which might result in elevated plasma cortisol, but ineffective cortisol function.

CONCLUSIONS

The diagnosis of adrenal insufficiency in the critically ill patient continues to be dogged by controversy and the role of steroids in the septic critically ill patient remains unclear. We suggest that the following caveats be borne in mind.

Firstly, the gold standard for the diagnosis of adrenal insufficiency in the critically ill patient has not been established. Secondly, caution must be exercised when interpreting a single plasma cortisol value. In the event of a single result indicating adrenal hypofunction, we suggest repeating the measurements after a 6 to 12 hour interval. The clinician must also be aware of the variations in cortisol concentration induced by the assay. Thirdly, the conventional high dose corticotrophin test has limitations. We further suggest that plasma free cortisol is more relevant than total plasma cortisol in the assessment of adrenal function in critical illness and that the low dose corticotrophin test is more sensitive than the conventional high dose testing. These areas should be the subject of further investigations.

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