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Journal club critique

Measurements of Serum Free Cortisol in Critically Ill Patients

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Expanded Abstract

Citation

Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. NEJM. 2004;350:1629-38.

Background

Because more than 90 percent of circulating cortisol in human serum is protein-bound, changes in binding proteins can alter measured serum total cortisol concentrations without influencing free concentrations of this hormone.

Hypotheses

Patients with presumably normal adrenal function but decreased cortisol-binding proteins will have lower-than-expected concentrations of serum total cortisol but appropriately elevated free cortisol levels.

Measurement of serum free cortisol concentrations will identify patients with normal or even increased adrenal function, who, on the basis of low total cortisol concentrations, would otherwise have been incorrectly considered to have adrenal insufficiency.

Methods

Setting: Medical, surgical, and cardiac ICUs and general medical ward of a tertiary care U.S. academic medical center.

Patients and Measurements: Baseline serum total cortisol, cosyntropin-stimulated serum total cortisol, aldosterone, and free cortisol concentrations were measured in 66 critically ill patients with an APACHE score of 15 or higher, 33 healthy volunteers, and 7 patients with adrenal insufficiency secondary to hypopituitarism. Patients were further divided into two groups based on their serum albumin concentrations of ≤ 2.5 g/dL (low albumin group, n=36) or >2.5 g/dL (normal albumin group, n=30).

Results

Baseline and cosyntropin-stimulated serum total cortisol concentrations were significantly lower in the low albumin group than the normal albumin group. However, serum free cortisol concentrations were similar in the two groups and were several times higher than the values in healthy controls. Fourteen of thirty-six (39%) low albumin patients had subnormal cosyntropin stimulated total cortisol concentrations, consistent with a traditional diagnosis of adrenal insufficiency. These same patients had high-normal or elevated serum free cortisol concentrations.

Conclusion

Nearly 40 percent of critically ill patients with hypoproteinemia had subnormal serum total cortisol concentrations, even though their adrenal function was normal. Measuring serum free cortisol concentrations in critically ill patients with hypoproteinemia may help prevent the unnecessary use of glucocorticoid therapy.

Commentary

The incidence of “adrenal insufficiency” in sepsis and septic shock is believed to be between 30 to 70%. Adrenal insufficiency is frequently characterized clinically as hypotension resistant to volume resuscitation and dependent on vasopressors. Two studies in the 1990’s showed that the use of stress doses of hydrocortisone decreased the duration of vasopressor therapy and improved shock reversal.[1,2] In 2002, a large multicenter, randomized, placebo controlled trial demonstrated that steroids improved mortality in patients with septic shock who had relative adrenal insufficiency, defined as an increase in total cortisol ≤ 9 μg/dL in response to a 250 μg cosyntropin stimulation test.[3] This has formed the basis for the current practice of treating patients with septic shock and adrenal insufficiency with stress doses of steroids.

However, there is controversy about the best indicator of adrenal insufficiency in the critically ill patients. Several criteria have been suggested, including, total cortisol ≤ 18μg/dL or change in total cortisol ≤ 9 μg/dL in response to cosyntropin stimulation test, and total random cortisol level ≤ 25 μg/dL.

Free cortisol is the physiologically active form of the hormone. In a healthy person, 10% of the cortisol is present in the free form, 20% is bound to albumin, and 70% is bound to cortisol binding globulin. Earlier studies have demonstrated that after a stressor like surgery, the concentration of cortisol binding globulin decreases by 50%, total cortisol levels increase by 55-100%.[4,5] However, surrogate markers of free cortisol, such as the free cortisol index (FCI), and calculated free cortisol levels increase by 130 to 600%. Importantly, these methods of free cortisol determination do not take into account the changes in serum albumin levels that occur in critical illness.

The current study by Hamrahian et al. demonstrates significant variability in serum total cortisol levels in the presence of hypoproteinemia. It shows that up to 39% of patients with low albumin levels would be misdiagnosed as being adrenally insufficient based on total cortisol levels. Levels in these patients appear to be low due to hypoproteinemia. Their free cortisol levels seem to be preserved and may in fact be elevated.

There are several important limitations of this study that deserve consideration. This study included 18 patients with sepsis but none with septic shock or multi-organ dysfunction; i.e., the patients most likely to benefit from corticosteroid administration were excluded. Because of this omission, it is difficult to know how to apply the present findings to this clinically important group. Furthermore, the physiological status of study patients at the time of cortisol measurements was not well defined, which makes it difficult to determine how free cortisol levels equate with other clinical parameters. Additionally, the technique for measuring free cortisol is difficult and expensive and not widely available. Finally, no standard levels of free cortisol have been reported, so the definition of abnormal for this parameter remains uncertain.

Like many studies, this one raises a number of interesting questions. First, what is the true incidence of adrenal insufficiency in the critically ill? Second, if we are not measuring and treating *true* adrenal insufficiency in septic hypoproteinemic patients, then what are we treating? Third, how does one reconcile the mortality benefit seen in the study by Annane and colleagues,[3] which used change in total cortisol to discriminate responders from non-responders? Finally, does free cortisol really matter? CORTICUS, an ongoing 800-patient multicenter trial, should help to answer these important questions. CORTICUS will test the hypothesis that low dose steroids improves 28-day mortality in patients with septic shock whose cortisol levels do not increase by more than 9 μg/dL in response to corticotropin stimulation.[6] In addition, the investigators will compare total and free cortisol levels in these patients.

Recommendation

Until CORTICUS is completed, we recommend that a) all patients in septic shock with ≤ 9 μg/dL total cortisol response to corticotropin stimulation receive low-dose corticosteroids, and b) free cortisol levels should not be used to determine adrenal responsiveness.

Competing interests

The authors declare that they have no competing interests.

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