Endocrine (1995) 3, 315–318
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Pituitary-adrenal axis function in systemic inflammatory response syndrome

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This study characterizes the hypothalamic-pituitary-adrenal axis function in patients with sepsis syndrome now known as systemic inflammatory response syndrome (SIRS). One hundred and thirteen patients with SIRS had their pituitary-adrenal axis tested with the use of a 250 μg IV ACTH stimulation test. No patient received corticosteroids prior to the ACTH stimulation test. Serum cortisol concentrations were measured prior to and 30 and 60 min after ACTH administration. 26% of the patients had bacteremia, 22% bacteruria, 22% AIDS, 17% renal failure, 15% diabetes, 13% severe liver disease, 8% GI bleed, 4% pancreatitis, 3% trauma and 1% classical Addison's disease. Several patients had more than one disorder. The overall mortality was 28%. Multivariate analysis identified that both the baseline cortisol concentration and delta cortisol concentration were significant indicators of mortality. Despite the fact that mortality was double in the bacteremic patients, the baseline cortisol concentrations were similar to the non-bacteremic patients (25.4 ± 1.9 *vs* 25.1 ± 2.5 μg/dl). The only cortisol abnormality noted in the bacteremic patients was a significantly smaller delta cortisol response to ACTH (14.7 ± 2.2 *vs* 18.9 ± 1.2 μg/dl; $P < 0.05$). These data imply that bacteremic processes may alter the adrenal responsiveness to intravenous ACTH administration. Understanding the pathophysiological disturbances responsible for an impaired adrenal reserve may identify new treatment strategies for patients with bacteremia.

Keywords: Addison's disease; cortisol; hypothalamic-pituitary-adrenal axis function; sepsis; AIDS; bacteremia

Introduction

Increased baseline cortisol concentrations in acute injury have been seen in most patients with a normal functioning hypothalamic-pituitary-adrenal axis. The greater the baseline cortisol concentration the higher the mortality in critically ill patients (Sibbald *et al.*, 1976; Jurney *et al.*, 1987). However, not all studies have demonstrated that a baseline serum cortisol is directly correlated with mortality (Sandberg *et al.*, 1956; Schein *et al.*, 1990; Rothwell *et al.*, 1991). In fact, Schultz *et al.* (1993) have demonstrated that a cortisol level less than 10 μg/dl was the best predictor of mortality due to cardiac arrest. In that study, a failure to attain a cortisol concentration of less than 30 μg/dl was associated with a 100% mortality. This would suggest that ability of a baseline cortisol level to predict outcome may be different for different diagnoses seen in the ICU setting.

A delta cortisol response of less than 9 μg/dl after ACTH administration in patients with septic shock is a better predictor of mortality than a baseline cortisol concentration (Rothwell *et al.*, 1991). In that study, the average cortisol increased above baseline by only 7 μg/dl in the non-survivors and 19 μg/dl in the survivors. The importance of adrenal cortisol responsiveness has also been reported in patients with acute bacterial infections by Sibbald *et al.* (1976). Mortality is nearly doubled in those patients who fail to increase their cortisol 13 μg/dl compared to those who increased their cortisol by 13 μg/dl or greater. Such data initiated the hypothesis that a blunted cortisol response (<13 μg/dl) after an ACTH test represents a form of adrenal dysfunction.

Adrenal crisis is a rare disorder that is seen in less than one in 10 000 hospital admissions. One exception to this observation has been the relative increase incidence of adrenal dysfunction in patients with tuberculosis. Up to 55% of patients in one study had a cortisol response less than 200 nmol/L (7.2 μg/dl) after intravenous ACTH (250 μg) (Ellis & Tayoub, 1986). Occult adrenal insufficiency has recently been shown to occur in approximately 8% of adults admitted to hospital with acute tuberculosis. (Barnes *et al.*, 1989). Critically ill patients have less than a 1% incidence of adrenal insufficiency (Jurney *et al.*, 1987; Span *et al.*, 1992). In comparison, two small studies suggested that between 10 to 20% of patients, with non-tuberculosis types of infections have adrenal insufficiency (Sibbald *et al.*, 1976; Rothwell *et al.*, 1991).

The purpose of this study was three-fold: (1) to determine if the delta cortisol concentration was an independent indicator of hospital survival; (2) to determine if an ACTH stimulated cortisol increase less than 13 μg/dl above baseline was associated with increased mortality; and (3) to document the incidence of adrenal insufficiency (cortisol less than 20 μg/dl after ACTH administration) in a large patient population with SIRS.

Results

Thirty percent of the 113 patients in the study were female. 107 of these patients had an ACTH-stimulated cortisol greater than 19.9 μg/dl. One patient was excluded from the data analysis because her baseline cortisol concentration was an outlier (228 μg/dl). Patient characteristics are listed in Table 1. The baseline serum cortisol concentration of the population of patients with SIRS was 25.1 ± 1.2 μg/dl (mean ± SEM) from which it increased to 34.7 ± 1.6 at 30 min and 43.0 ± 1.5 at 60 min. Six patients had a serum cortisol response of <20 μg/dl measured at both 30 and

Table 1 Patient characteristics

	Normal adrenal response (ACTH stimulated cortisol ≥ 20)	*Rule-Out adrenal insufficiency (ACTH stimulated cortisol < 20 μg/dl)*
(n)	106	6
Age (years)	49 ± 2	41 ± 3*
Sex (M/F)	75/32	4/2
Ht (inches)	66 ± 1	66 ± 2
Wt (pounds)	143 ± 4	144 ± 14
IBW (%)	101 ± 3	106 ± 12
APACHE II	10.7 ± 0.6	6.2 ± 2.2
Albumin (g/dl)	2.64 ± 0.08	3.32 ± 0.91*

Mean ± SEM; *$P < 0.05$ by paired *t*-test.

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Received 23 August 1994; accepted 13 December 1994

60 min after ACTH administration. In this group of 'rule out' adrenal insufficiency, the mean cortisol at baseline was 6.0 ± 2.4 μg/dl and increased to 10.2 ± 0.5 at 30 min and 15.8 ± 0.5 at 60 min. Only one patient had signs of adrenal insufficiency (hypotension, hyperkalemia and hyponatremia). This patient, and one other of the six patients were treated with glucocorticoid therapy. None of the treated patients expired. One of the four non-treated patients expired. The six patients were younger and had a higher serum albumin level than the larger group (Table 1).

The hospital mortality of the 106 patients with SIRS was 28%. Women and men had a similar mortality rate (27.8 *vs* 27.1%). The mortality rate increased to 44% in 27 patients who were blood culture positive. The mean age, Apache II score, serum albumin, baseline cortisol and delta cortisol were significantly different in those who died compared to those who survived (Table 2). Twenty-three patients had a baseline cortisol less than 15 μg/dl and only one of these patients expired. Baseline cortisol and delta cortisol were not significantly inversely correlated with each other ($r = -0.14$) so that both variables were used as independent variables.

Baseline cortisol concentrations were higher in renal failure patients who did not survive (30.4 ± 3.0 *vs* 20.3 ± 2.2, $P < 0.05$). However, baseline cortisol concentrations were not elevated in patients with bacteremia who died compared to those with bacteremia who survived (26.9 ± 3.1 *vs* 24.1 ± 2.4 μg/dl, respectively). This was also true for patients with additional diagnoses of diabetes (25.8 ± 6.2 *vs* 25.2 ± 3.2 μg/dl) and AIDS (19.8 ± 2.5 *vs* 25.0 ± 3..2 μg/dl, respectively). Nevertheless, the baseline cortisol concentration was significantly correlated with hospital mortality ($r = 0.940$; $P < 0.01$, Figure 1). However, the baseline cortisol concentration was not elevated in the blood culture positive patients compared to all of the non-bacteremic patients (25.4 ± 1.9 *vs* 25.1 ± 2.5 μg/dl; respectively). The only cortisol abnormality noted in the bacteremic patients was a significantly smaller delta cortisol response to ACTH (14.7 ± 2.2 *vs* 18.9 ± 1.2 μg/dl; $P < 0.05$).

The delta cortisol response was significantly inversely correlated with hospital mortality ($r = -0.727$; $P < 0.01$). The division of the cortisol response into groups of (1) less than 13 μg/dl, (2) 13 to 25.9 μg/dl, and (3) equal to or greater than 26 μg/dl demonstrates a significant relationship with hospital mortality (Figure 2). This 'blunted' response was most likely secondary to the higher baseline cortisol concentration since maximal cortisol concentrations were similar in the survivors and non-survivors.

Stepwise logistic regression analysis identified that Apache II, baseline cortisol, serum albumin, delta cortisol and renal disease were all variables that significantly predicted mortality. The use of age, sex, weight as a percent of ideal body weight, presence of AIDS, cancer or diabetes did not improve the predictability of the patients outcome. Table 3 demonstrates the coefficients, the standard error of the coefficients, and the significance level for each of the variables. Improvements in the chi-square analysis can be seen mostly for the Apache II score and the baseline cortisol concentration. The additive use of serum albumin, delta cortisol response and renal failure also significantly improved the ability to predict outcome. Baseline cortisol, renal failure, delta cortisol and albumin also predicted mortality in the absence of knowing the Apache II score.

Discussion

The model to predict mortality identified that a combination of Apache II score, baseline cortisol, albumin, delta cortisol

Table 2 Demographic and biochemical data in survivors and non-survivors

	Survivors	*Non-Survivors*
Age (years)	47 ± 2	53 ± 3*
Apache II	8.9 ± 0.6	14.5 ± 1.1*
IBW (%)	99 ± 3	103 ± 7
Albumin (gm/l)	28.1 ± 0.9	21.8 ± 1.3*
Baseline cortisol (μg/dl)	22.1 ± 1.2	32.2 ± 2.9**
Delta cortisol (μg/dl)	19.7 ± 1.3	13.2 ± 1.6**
Maximum cortisol (μg/dl)	41.9 ± 1.6	46.1 ± 3.2

Mean ± SEM; *$P < 0.05$, **$P < 0.01$ by *t*-test.

Table 3 Multivariate analysis with stepwise logistic regression to predict mortality in patients with SIRS

Variable	*Coefficient*	*Standard error*	*Improvement in Chi-Square*	P-*value*
Apache II	−0.1024	0.0492	15.4	0.000
Baseline cortisol	−0.0487	0.0226	7.5	0.002
Serum albumin	0.1041	0.0321	5.7	0.017
Delta cortisol	0.0752	0.0330	5.1	0.024
Renal failure	−1.5970	0.7360	5.0	0.025

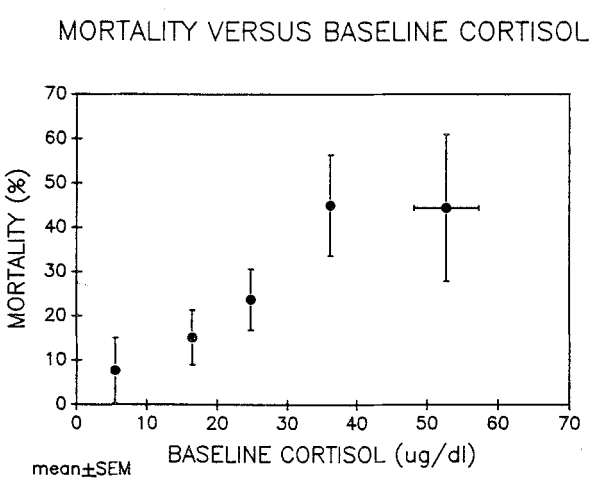

Figure 1 In the population of patients with SIRS, the baseline cortisol was significantly correlated with the hospital mortality rate up to a level of approximately 40 μg/dl. The baseline cortisol was subdivided into intervals: 0–10, 11 to 20, 21 to 30, 31 to 40 and greater than 40 μg/dl. The data is represented as mean ± SEM.

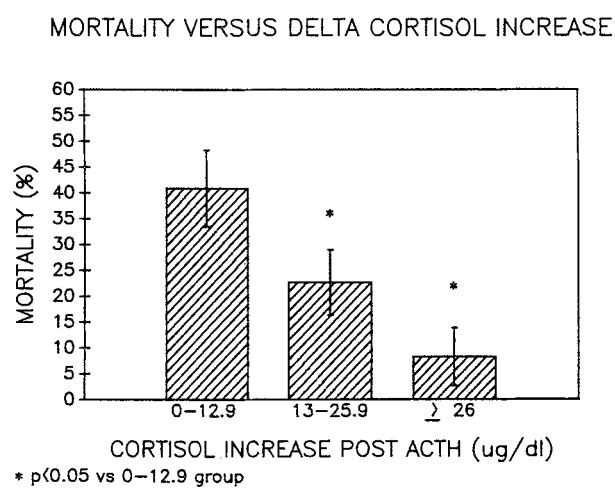

Figure 2 This figure demonstrates the mortality rate compared to the maximum amount of the delta cortisol increase after an ACTH stimulation test. The delta cortisol response was subdivided into intervals of (1) 0 to 12.9, (2) 13 to 25.9, and (3) greater than 25.9 μg/dl. It is noted on this figure that the mortality rate is at its lowest in those patients who can release the largest amount of cortisol during an ACTH test. The data are represented as mean ± SEM. *$P < 0.05$ by chi-square testing.

and renal failure best predicted mortality in the overall group. Exclusion of the Apache II score also identified that delta cortisol and baseline cortisol were both important predictors of hospital mortality. However, our data failed to identify that the delta cortisol response provided more information than a baseline cortisol concentration in non-bacteremic patients. In fact, the lower response may be secondary to the higher baseline concentration. The unique finding was the similar baseline cortisol concentrations in the bacteremic patients. In this subgroup, the delta cortisol response provided more information than a baseline cortisol concentration.

The association of diminished adrenal reserve and mortality in patients with bacteremia may reflect a primary adrenal abnormality, pituitary dysfunction or a secondary phenomena due to a metabolic response to injury (Reincke *et al.*, 1994).

Corticostatins are a family of structurally related proteins that act in rabbits to directly inhibit adrenal ACTH binding and corticosterone production (Zhu & Solomon, 1992). Corticostatin concentrations increase 20-fold in rabbits plasma, 10 fold in adrenal tissue and five-fold in the hypothalamus during systemic infection (Tominaga *et al.*, 1992). Even though the exact regulatory nature is not known, it is possible that corticostatin may have been responsible for the blunted cortisol response observed in our bacteremic patients. Both a lower baseline cortisol and a blunted cortisol response might be explained by corticostatins acting at the site of the adrenal glands. Further research is in progress to test this hypothesis.

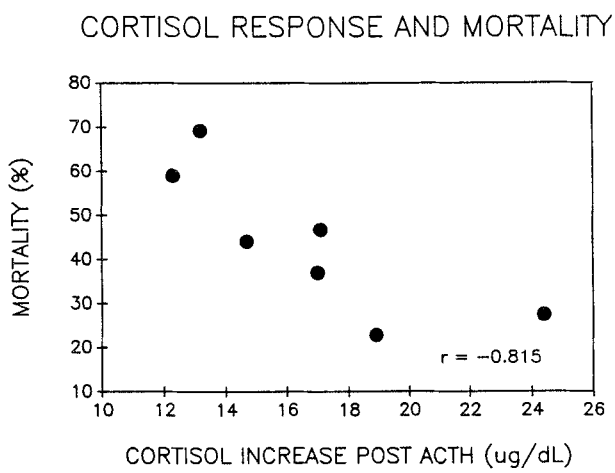

Figure 3 This figure combines the data from Table 4 in a graphical representation comparing the individual published papers for mean delta cortisol response compared to mean hospital mortality. If the paper had two groups the overall mean was determined for baseline cortisol, delta cortisol response and mortality. The bacteremic patients in the current study were seperated from the non-bacteremic patients. It can be seen that there is an inverse correlation between delta cortisol response and mortality in patients with sepsis/SIRS ($r = -0.815$; $P<0.05$; $Y = -0.201*X + 25.6$). If the same data are plotted as baseline cortisol concentration versus mortality, there is no significant relationship ($r = -0.377$).

Besides corticostatins, tumor necrosis factor alpha (TNF) has been implicated in the regulation of hypothalamic-pituitary-adrenal axis function (Marano *et al.*, 1990; Reincke *et al.*, 1994). TNF can blunt the normal response to corticotropin releasing hormone, growth hormone releasing hormone, luteinizing hormone and prolactin in rat pituitary cells (Gaillard *et al.*, 1990). TNF has also been demonstrated to inhibit the p450 enzymes responsible for cortisol production in fetal adrenal cells (Jaattela *et al.*, 1991). However, the majority of the published evidence indicates that TNF-alpha and IL-1 stimulate the hypothalamic-pituitary-adrenal axis acting at a site above the pituitary (Kakucska *et al.*, 1993; Watanobe & Takebe, 1993). IL-6 may also be involved with this activation (Perlstein *et al.*, 1993). TNF-alpha administration in humans can acutely increase ACTH release and increase serum cortisol (Michie *et al.*, 1988) so that there is little evidence that TNF could be responsible for the reduced cortisol response in bacteremic patients.

Acute illness such as seen in bone marrow transplantation is associated with the euthyroid sick syndrome with a reduction in thyroxine, triiodothyronine, thyrotropin and an elevation in reverse triiodothyronine. This response is due in part to a decrease in thyrotropin secretion (Wehmann *et al.*, 1985). Serious illness or starvation is associated with gonadotropin deficiency (Woolf *et al.*, 1985). Both of these responses may have survivability benefits by reducing energy expenditure and fertility while critically ill. However, the loss of ACTH secretion has no survival advantage. ACTH concentrations have been demonstrated to be normal or elevated in major illnesses so that a reduced concentration was considered unlikely (Drucker & Shandling, 1985, Schultz *et al.*, 1993). Because of the interesting results observed in the blood culture positive patients, further work will be required to evaluate the hypothalamic-pituitary axis.

Patients with bacteremia have a higher mortality than non-bacteremic patients as shown by us and others (Jurney *et al.*, 1987). In our study, patients with bacteremia had a similar baseline cortisol concentration compared to non-bacteremic patients. However, the delta cortisol response was significantly lower and the mortality rate significantly higher. Patients with bacteremia may not have an increase baseline cortisol yet their mortality is greater (Table 4: Rothwell, 1991, Sibbald *et al.*, 1976; Jurney *et al.*, 1987), when compared to what might be expected based on the relationship between mortality and baseline cortisol (Figure 1). Evaluating the published data in Table 4, baseline cortisol was not correlated with mortality ($r = -0.377$). In the bacteremic patients, the delta cortisol response and the maximum cortisol concentration after ACTH were both significantly smaller (Table 4). The delta cortisol response to ACTH was significantly inversely correlated with mortality ($r = -0.815$, $P<0.05$, Figure 3). Bacteremic patients may

Table 4 Delta cortisol response post ACTH and hospital mortality in SIRS

Primary DX	*Sample size* (n)	*Baseline cortisol*	*Delta cortisol*	*Maximum cortisol*	*Mortality %*	*References*
Sepsis	26	27.7	13.2±2.8	40.9	69.2	Sibbald
Sepsis	32	26.1	12.3±1.8	38.4	59.0	Rothwell
Sepsis	27	25.4	14.7±2.2	40.1	44.4	Tayek
Mean Sepsis		26.4	13.4*	39.8*	57.5*	
SIRS	30	35.7	17.1±1.6	52.8	46.7	Wade
ICU-Patients	70	35.3	17.0±3.0	52.3	37.0	Jurney
SIRS	79	25.1	18.9±1.2	44.0	22.8	Tayek
SIRS	40	44.7	24.4±3.3	69.1	27.5	Drucker
Mean SIRS		35.2	19.3	54.5	33.5	

Mean ± SEM; *$P<0.05$ by *t*-test.

represent a unique type of injured patient where adrenal dysfunction may be present.

Despite the fact that the incidence of Addison's disease is rare in SIRS, the finding of a baseline serum cortisol less than 15 μg/dl in acute illness may be concerning to many clinicians. Recently Kidess *et al.* (1993) have reported three critically ill hypotensive patients with reduced baseline cortisol concentration (<14 μg/dl) and ACTH stimulated cortisol concentrations greater than 20 μg/dl who clinically improved with glucocorticoid treatment (1993). In our patient population, 23 patients had a baseline cortisol concentration less than 15, and only one of these patients expired. Because the mortality rate was the lowest for the group with the lowest baseline serum cortisol concentration (Figure 2), it would seem that a low cortisol concentration in SIRS does not indicate adrenal dysfunction.

In summary, these data document that classical Addison's disease is rare in SIRS. Bacteremic patients with a blunted cortisol response to intravenous ACTH identifies a sub-group of patients with an increased mortality. In those few studies of bacteremic patients where adrenal response and mortality have been reported, there appears to be a direct correlation between the delta cortisol response and survival (Table 4, Figure 3). Our large study confirmed earlier research in bacteremic patients which suggest the need for development of treatment protocols for bacteremic patients who have a blunted cortisol response to ACTH. The 'blunted' response observed in the non-bacteremic patients may be due to their higher baseline values since the maximum concentrations were similar between the survivors and non-survivors. A prospective study to evaluate the need for glucocorticoid therapy in bacteremic patients with a blunted adrenal function should be considered.

Methods

113 patients with systemic inflammatory response syndrome (SIRS) were evaluated for adrenal function with the standard Cortrosyn Stimulation Test (250 μg ACTH IV push). The average age of the population of 113 patients studied was 49 ± 2 (mean ± SEM) and the Apache II score was 10.7 ± 0.6 (Knaus *et al.*, 1986). All patients met the criteria for the SIRS diagnosis (Bone *et al.*, 1992). The patient diagnosis included 26% with bacteremia, 22% with bacteruria, 22% with AIDS, 17% with renal failure, 15% with diabetes, 13% with severe liver disease, 8% with GI bleed, 4% with pancreatitis and 3% with trauma. Several patients had more than one disorder. The ACTH stimulation test was performed in the emergency room or hospital setting. Patients with a known history of prior steroid usage, adrenal insufficiency or congenital adrenal hyperplasia were not included in the study.

Serum cortisol was measured at time 0 prior to ACTH and 30 and 60 min after ACTH was administered by IV push (250 μg ACTH, Cortrosyn, Organon Inc, West Orange, NJ). Serum cortisol levels were measured by a standardized antibody coated tube RIA assay (Farmer & Prince, 1974). The intra assay CV for low, medium and high concentrations were 12.3%, 3.9% and 3.0% respectively. The inter assay CV was 14.7%, 9.1% and 7.5% respectively.

One patient who expired was eliminated from the final data analysis due to her baseline cortisol being a outlier (228 μg/dl). The remaining data was normally distributed. Data analysis was performed by t-testing, chi square analysis, and linear regression analysis by least squares fit with the statistical package of BMDP. To identify all factors that might have contributed to mortality, a multivariate analysis was performed using stepwise logistic regression of equally weighted variables: age, sex, body weight as percent of ideal, serum albumin, baseline cortisol, delta cortisol, Apache II, and the presence or absence of renal failure, AIDS, diabetes or cancer. Significance was $P<0.05$.

Acknowledgements
Grants supported in part by the Pfeiffer Research Foundation.

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