Intensive Care Med (2004) 30:1216–1219
DOI 10.1007/s00134-004-2297-2

BRIEF REPORT

Ioanna Dimopoulou
Stylianos Tsagarakis
Evangelia Douka
Maria Zervou
Andreas T. Kouyialis
Urania Dafni
Nikolaos Thalassinos
Charis Roussos

The low-dose corticotropin stimulation test in acute traumatic and non-traumatic brain injury: incidence of hypo-responsiveness and relationship to outcome

Received: 12 July 2003
Accepted: 23 March 2004
Published online: 21 April 2004

I. Dimopoulou (✉) · E. Douka · M. Zervou · A. T. Kouyialis · U. Dafni · C. Roussos
Department of Critical Care Medicine, Evangelismos Hospital, Medical School, National and Kapodistrian University of Athens, 10675 Athens, Greece
e-mail: idimo@otenet.gr
Tel.: +30-210-6200663
Fax: +30-210-6202939

S. Tsagarakis · N. Thalassinos
Department of Endocrinology, Diabetes & Metabolism, Evangelismos Hospital, Medical School, National and Kapodistrian University of Athens, 10675 Athens, Greece

Present address:
I. Dimopoulou, 2 Pesmazoglou Street, 14 561 Kifissia, Athens, Greece

Abstract *Objective:* To investigate adrenal responses to the low-dose corticotropin (ACTH) stimulation test in acute traumatic or non-traumatic brain injury (BI) and to assess its value in predicting outcome. *Design:* Prospective study. *Setting:* Intensive care unit (ICU) in a university hospital. *Patients and participants:* Seventy-five patients with acute BI, with a median age of 45 years were investigated. BI was due to trauma (n=51), ischemic stroke (n=17), subarachnoid hemorrhage (n=4) or intracerebral hemorrhage (n=3). *Interventions:* Blood was taken on day 16 (median) after admission to the ICU to determine baseline cortisol and ACTH. Thereafter, a low-dose stimulation test (LDST) was performed: 1 μg of tetracosactrin was injected and 30 min later a second blood specimen was obtained to measure stimulated cortisol. Patients having a stimulated cortisol below 500 nmol/l were defined as non-responders to the LDST. *Measurements and results:* Median baseline and stimulated cortisol were 491 nmol/l and 690 nmol/l, respectively. The median increment in cortisol was 154 nmol/l (range 5–579 nmol/l). Mean ACTH was 46±21 pg/ml. Ten (13%) patients were non-responders to the LDST; these had a higher mortality rate compared to patients with adequate cortisol production (70 vs 32%, p=0.034). Logistic regression analysis revealed that APACHE II (p<0.001), Glasgow Coma Scale (GCS) (p=0.04) and age (p=0.02) were independent outcome predictors. In contrast, the increment in cortisol (p=0.26) did not add to outcome prediction. *Conclusions:* Adrenal hypo-responsiveness in the setting of acute traumatic or non-traumatic BI is not an independent outcome predictor in the presence of high APACHE II, low GCS and older age.

Keywords Head trauma · Stroke · Critical illness · Cortisol · Low-dose corticotropin stimulation test · Outcome prediction

Introduction

Severe illness is accompanied by activation of the hypothalamic-pituitary-adrenal (HPA) axis, as demonstrated by increased corticotropin (ACTH) and cortisol concentrations. High cortisol levels have a vital role in maintaining vascular tone and endothelial integrity, and in potentiating the vasoconstrictive action of the catecholamines [1].

Impairment in the normal corticosteroid response is now increasingly recognized in critical illness [2]. Some investigations point to a relation between adrenocortical dysfunction and mortality in severe illness [3], whereas others do not [4]. Mechanisms regulating adrenocortical secretion are in the cranial cavity and acute brain injury (BI) as a result of trauma, hemorrhage or ischemia might be expected to disturb these mechanisms. Thus, recently we showed that a proportion of patients with head trauma

may have diminished cortisol production due to primary adrenal dysfunction or to hypothalamic-pituitary failure [5].

The standard stimulation test using 250 μg of ACTH is the most widely used diagnostic test for the detection of adrenocortical insufficiency [6]. During the last decade it has been shown that 1 μg is the lowest ACTH dose that causes maximal adrenal stimulation [7]. The use of a supra-physiological dose may lead to false-positive cortisol responses and may cause the diagnosis of partial hypoadrenalism to be missed, because it provides extremely high plasma ACTH concentrations [7]. The results of the low-dose stimulation test (LDST) correlate with those of the insulin-induced hypoglycemia test [8], the generally agreed reference standard for the evaluation of the HPA axis [6], and are superior to those of the high-dose ACTH test in detecting subtle defects of adrenal reserves [9]. This test has been previously used in critical illness [10].

To further expand our knowledge on adrenocortical function in traumatic and non-traumatic BI, we measured cortisol levels before and after stimulation with the LDST during ICU stay. Our objective was: (a) to assess the incidence of adrenocortical dysfunction and (b) to investigate whether cortisol responses predict outcome.

Materials and methods

Study population

This study included 75 consecutive patients with BI necessitating admission to the ICU. Patients receiving medications known to interfere with the HPA axis were excluded [1, 2]. Outcome was defined as survival or death in the ICU. The institutional review board approved the study and informed consent was obtained from patients' relatives.

Endocrine evaluation

Morning blood was taken for determination of baseline cortisol and ACTH. Thereafter, a LDST was performed: 1 μg of freshly prepared tetracosactrin (Synacthene, Novartis, Basel, Switzerland) was injected as a bolus, and 30 min later a second blood specimen was obtained for measurement of stimulated cortisol. Patients having stimulated cortisol concentrations below 500 nmol/l were defined as non-responders to the LDST [1].

Assays

Plasma cortisol was determined by a sensitive immunofluorometric assay (Chiron, East Walpole, MA) (normal morning values for unstressed individuals: 138–690 nmol/l). The assay has a detection limit of 5.5 nmol/l and intra-assay coefficients of variation of 8.0%, 6.4% and 9.2% at cortisol concentrations of 150 nmol/l, 410 nmol/l and 877.1 nmol/l, respectively. ACTH was measured by a highly specific immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA) (normal values: 9–52 pg/ml). Inter- and intra-assay coefficients of variation were 8% and 4%, respectively.

Statistical analysis

An initial assumption was made that 25% of the patients will be non-responders to the LDST with a corresponding mortality rate of 70%. A sample size of 74 is needed to detect, with a power of 80%, a two-fold decrease in mortality rate in responders as compared to non-responders, with a two-sided test at the significance level of 5%. The data are presented as means ± SD or medians and ranges. Comparisons between the groups were performed by Mann-Whitney U test or Fisher exact test. Spearman's correlation coefficient assessed the relationships between variables. Differences were considered significant at p less than 0.05. Logistic regression analysis with death as an outcome was performed with the following possible prognostic factors: age, sex, GCS on admission in the ICU, APACHE II score on the day of endocrine evaluation, multiple trauma, duration of critical illness as expressed by the study day and increment in cortisol (stimulated minus baseline cortisol). Non-significant variables were deleted by backward elimination (deletion criterion $p>0.05$).

Results

Seventy-five (58 men) brain-injured patients with a median age of 45 years (range 15–80 years) were enrolled. Brain injury was due to trauma (n=51), ischemic stroke (n=17), subarachnoid hemorrhage (n=4) or intracerebral hemorrhage (n=3). GCS on admission to the ICU ranged from 4 to 13 (median: 7). APACHE II score on the day of endocrine evaluation ranged from 4 to 23 (median: 9). In view of the paucity of data regarding the responsiveness to the LDST in BI patients, endocrine assessment was performed at several time points following ICU admission: days 1–7, n=18; days 8–14, n=10; days 15–22, n=22; days 23–30, n=13, days 31–60, n=9. Median baseline and stimulated cortisol concentrations were 491 nmol/l (range 124–2,191 nmol/l) and 690 nmol/l (range 171–2,208 nmol/l), respectively. The median increment in cortisol was 154 nmol/l (range 5–579 nmol/l). Baseline and stimulated cortisol were significantly related (r=0.76, $p<0.005$). Mean ACTH was 46±21 pg/ml (n=45). Albumin was 2.9±0.5 g/dl (range 1.8–4.2 g/dl). In ten (13%) patients stimulated cortisol concentrations were below 500 nmol/l. The clinical characteristics and hormonal studies of responders and non-responders to the LDST are shown in Table 1. Responders had higher baseline and stimulated plasma cortisol levels. Similarly, the increment in cortisol was higher in responders. A higher mortality rate was observed in non-responders compared to responders (Table 1).

Logistic regression analysis revealed that significant predictors of death were APACHE II (odds ratio =1.46, 95% C.I. 1.22–1.75, $p<0.001$), GCS (odds ratio =1.04, 95% C.I. 1.03–1.09, p=0.04), and age (odds ratio =1.05, 95% C. I. 1.01–1.10, p=0.02). The odds ratio of 1.46 in APACHE II indicates a 46% increase in the probability of dying per one unit increase in the scoring system. In contrast, sex (p=0.70), multiple trauma (p=0.10), duration

Table 1 Clinical characteristics and hormonal studies in responders and non-responders to the low-dose stimulation test. Values are medians with ranges in parentheses, unless otherwise designated

	Responders	Non-responders	*p* value
	(*n*=65)	(*n*=10)	
Age (years)	45 (15–75)	51 (25–80)	NS
Sex (M/F)	49/16	9/1	NS
Type of brain injury			
Traumatic (*n*)	43	8	NS
Non-traumatic (*n*)	22	2	
Day of endocrine assessment after admission to the ICU	15 (1–54)	22 (3–60)	NS
GCS score	7 (4–13)	8 (4–13)	NS
APACHE II score	8 (4–23)	14 (4–22)	NS
Baseline cortisol (nmol/l)	505 (229–2,191)	306 (124–422)	<0.001
Stimulated cortisol (nmol/l)	720 (496–2.208)	381 (171–472)	<0.001
Increment in cortisol (nmol/l)	163 (5–580)	63 (8–166)	0.002
Percent increment in cortisol	26±14	20±13	0.24
ACTH, pg/ml	40 (7–119)	55 (4–115)	NS
Mortality [*n* (%)]	21 (32%)	7 (70%)	0.034

GCS Glasgow Coma Scale, *ACTH* corticotropin, *NS* non-significant

of critical illness (p=0.69) and the increment in cortisol (p=0.26) did not add to outcome prediction.

Discussion

Acute traumatic BI may elicit abnormalities in the functional integrity of the HPA axis in about 25% of patients [11]. Similarly, abnormalities in the cortisol axis have been described in a substantial number of patients early after stroke [12]. In these studies the adequacy of cortisol secretion was examined by the high-dose (250 μg) ACTH stimulation test. In the present series the LDST was used to evaluate HPA axis activity in BI patients during the period of critical illness. Although based on data from normal non-stressed volunteers, a "normal" cortisol response to this test has been set at 18 μg/dl (500 nmol/l) [1]; there is increasing evidence that this cut-off correlates well with symptoms of relative adrenal insufficiency in severe illness and predicts a beneficial response to stress doses of glucocorticoids [10]. By using this cut-off level we found that 13% of BI patients presented with inadequate cortisol responses.

The mechanism of the impaired cortisol response in BI patients is currently unclear. A central defect is one possibility. However, in this study diminished cortisol responses were equally observed in the early and late phases following BI. Because ACTH deprivation of short duration may not be sufficient to induce adrenal atrophy, another possibility is that adrenal dysfunction may have developed in the context of critical illness, as recently described [2].

There has been much debate about the prognostic value of cortisol levels in severe illness. An inability to mount an adequate cortisol response has been found to increase the risk of death in septic shock [3], as seen in patients with adrenal suppression by corticosteroids [13] or etomidate [14]. In contrast, other studies failed to confirm the association between cortisol responses and mortality [4]. In line with this last report, we found that adrenal hypo-responsiveness in BI is not an outcome predictor in the presence of high APACHE II, low GCS and advancing age. The reasons for such conflicting results are currently unclear; they might be explained by the different criteria used to interpret the high- or low-dose ACTH stimulation tests and the patient populations studied.

The limitations of our study should be acknowledged. First, the ACTH stimulation tests were performed at different times with respect to ICU admission. Although we did not observe significant differences in cortisol responses depending on the time of testing, more research is needed to determine if our results are applicable in BI patients investigated in a predetermined time interval. Second, we did not measure cortisol-binding globulin (CBG). Patients in the ICU typically show an acute phase response associated with a substantial fall in CBG and a concomitant, high free cortisol index [15]. In such a situation the serum total cortisol might not reflect maximal HPA axis activity. However, CBG levels normalize within 7 days of the onset of critical illness [15]. The great majority (75%) of our patients were evaluated beyond this time period and, thus, it is likely that total cortisol is a satisfactory surrogate for adrenal function in the present study.

In conclusion, adrenocortical impairment in acute BI is not uncommon. This dysregulation does not represent an independent outcome predictor for mortality in the ICU.

References

1. Oelkers W (1996) Adrenal insufficiency. N Engl J Med 335:1206–1212
2. Cooper MS, Stewart PM (2003) Corticosteroid insufficiency in acutely ill patients. N Engl J Med 348:727–734
3. Rothwell PM, Udwadia ZF, Lawler PG (1991) Cortisol responses to corticotropin and survival in septic shock. Lancet 337:582–583
4. Boachour G, Tirot P, Gouello JP, Mathieu E, Vincent JF, Alquier P (1995) Adrenocortical function during septic shock. Intensive Care Med 21:57–62
5. Dimopoulou I, Tsagarakis S, Kouyialis AT, Roussou P, Assithianakis G, Christoforaki M, Ilias I, Sakas DE, Thalassinos N, Roussos C (2004) The hypothalamic-pituitary-adrenal axis in critically ill patients with traumatic brain injury: incidence, pathophysiology and relationship to vasopressor dependency and peripheral interleukin-6 levels. Crit Care Med 32:404–408
6. Grinspoon SK, Biller BMK (1994) Clinical Review 62. Laboratory assessment of adrenal insufficiency. J Clin Endocrinol Metab 79:923–931
7. Dickstein G, Shechner C, Nicholson WE, Rosner I, Shen-Orr Z, Adawi F, Lahav M (1991) Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day and suggested new sensitive low dose test. J Clin Endocrinol Metab 72:773–778
8. Ambrosi B, Barbetta L, Re T, Passini E, Faglia G (1998) The one microgram adrenocorticotropin test in the assessment of hypothalamic-pituitary-adrenal function. Eur J Endocrinol 139:575–579
9. Tordjman K, Jaffe A, Trostanetsky Y, Greenman Y, Limor R, Stern N (2000) Low-dose (1 microgram) adrenocorticotrophin (ACTH) stimulation as a screening test for impaired hypothalamo-pituitary-adrenal axis function: sensitivity, specificity and accuracy in comparison with the high-dose (250 microgram) test. Clin Endocrinol 52:633–640
10. Bourne RS, Webber SJ, Hutchinson SP (2003) Adrenal axis testing and corticosteroid replacement therapy in septic shock patients—local and national perspectives. Anaesthesia 58:591–596
11. Hoen S, Asehnoune K, Brailly-Tabart S, Mazoit JX, Benhamou D, Moine P, Edouard AR (2002) Cortisol response to corticotropin stimulation in trauma patients: influence of hemorrhagic shock. Anesthesiology 97:807–813
12. Olsson T, Marklund N, Gustafson Y, Nasman B (1992) Abnormalities at different levels of the hypothalamic-pituitary-adrenocortical axis early after stroke. Stroke 23:1573–1576
13. Salem M, Tainsh RE Jr, Bromberg J, Loriaux DL, Chernow B (1994) Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 219:416–425
14. Ledingham IM, Watt I (1983) Influence of sedation on mortality in critically ill multiple trauma patients. Lancet 1:1270
15. Beishuizen A, Thijs LG, Vermes I (2001) Patterns of corticosteroid-binding globulin and the free cortisol index during septic shock and multitrauma. Intensive Care Med 27:1584–1591