Plasma cortisol is often decreased in patients treated in an intensive care unit

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Abstract  Objective: To investigate the prevalence of adrenal hypofunction, as assessed by plasma cortisol (p-cortisol) and its relationship to clinical events.
Design: Prospective, consecutive.
Setting: General intensive care unit in a university hospital.
Patients: Fifty-five patients (34 men and 21 women) were studied (surgery 40 patients, hemodialysis 5, ventilator treatment 45, sepsis 21).
Methods: Morning basal levels of p-cortisol were determined. Previous reports define adrenal insufficiency to be present if p-cortisol under stressful conditions is lower than either 400 or 500 nmol/l. The tetracosactoid test (250 µg Synacthen) was performed in 16 patients and urinary 24-h excretion of cortisol in 24 (none on corticosteroid treatment).
Results: Median p-cortisol was 550 nmol/l (range 20–1764). In 36% of patients p-cortisol was lower than 400 nmol/l and in 47% lower than 500 nmol/l. There was a significantly increased probability (P < 0.05) of p-cortisol being below 400 nmol/l in patients admitted due to trauma or cerebral disorder and in patients on ventilator therapy or on mannitol. Thirty minutes after tetracosactoid administration p-cortisol response was lower than 200 nmol/l in 56% of the patients.
Conclusions: Several patients had low p-cortisol and attenuated responses to tetracosactoid, indicative of adrenal insufficiency. There seem to be certain risk factors for adrenal hypofunction which may justify more frequent use of physiological doses of corticosteroid in selected patients.

Key words  Intensive care · Sepsis · Surgery · Corticosteroid · Adrenal hypofunction · Cortisol · Trauma

Introduction

During severe sepsis or trauma there is an increase in the release of various toxins and cytokines, which increases the activity of the cascade systems. This process may progress into multiorgan failure and death [1]. The most severe stages may also include adrenal insufficiency [2, 3, 4]. However, there are conflicting data and controversies as to the expected concentrations of plasma cortisol (p-cortisol) and response to corticotropin in severely ill patients (see [5]). During surgical procedures such as laparotomy serum corticotropin and cortisol rise rapidly but usually return to baseline values within 24–48 h. The magnitude of the postoperative increase is positively correlated with the extent of surgery (see [6]), and after operation there is initially no circadian variation in serum cortisol.

During severe illness, in some studies, serum cortisol tends to be even higher. The values are highest in patients with the highest illness severity scores and in those with the highest risk of mortality, and the values are very high (828–7173 nmol/l) shortly before death [5, 6, 7]. However, others report that many patients have lowered basal cortisol concentrations or a poor response to the corti-
cotropin stimulation test [3, 5, 8, 9]. The overall incidence of adrenal insufficiency is reported to be 0.66% in the surgical intensive care unit (ICU). In patients with a stay of longer than 14 days in the ICU, 6% have been found to have adrenal insufficiency, and this proportion is even higher in older patients [10].

The question is how frequent a relative insufficiency is which may benefit from substitution therapy. Most studies of septic patients show high doses of steroids to be of no benefit [11, 12, 13], although a recent study using supraphysiological doses of hydrocortisone reported a favorable effect on survival [14]. Adrenal insufficiency is not consistently defined and various lower limits exist for basal cortisol and the extent of the increase after the corticotropin stimulation test (tetracosactoid test) [3, 10, 15, 16, 17, 18, 19, 20].

The aim of this study was to evaluate p-cortisol concentrations of patients in an ICU and to characterize patients at risk for adrenal insufficiency.

Materials and methods

The 55 patients included in the study were based on a consecutive series of severely ill patients admitted to the ICU with an expected stay of longer than 3 days. Excluded were patients on medication with steroids (n = 3) and those with minor ICU problems such as intoxication or uncomplicated postoperative general surgery, with an expected intensive care stay shorter than 3 days. Some of these patients had to stay longer than 3 days and were included here. There were no other exclusion criteria. Ethamidate was not used (not approved in Sweden). Relatives were informed and consented to the study. The median age of the patients was 55 years (range 1–79, mean 63). There were 34 men (62%) and 21 women.

In 16 of the patients a stimulation test with synthetic adrenocorticotrophic hormone, tetracosactoid (Synacthen) was performed to evaluate the adrenal response. In six of these the initial p-cortisol was achieved by the test. Elective surgery had been performed in 13 and acute surgery in 27 before admission to the ICU. In 14 of these patients surgery was performed due to aortic aneurysm. Fifteen of the patients had not been treated by surgery. Cerebral affection (e.g., hemorrhage, encephalitis, and meningitis) was present in 20 of the patients (diagnosis lacking in one). A cerebral trauma was the reason for treatment in nine. Trauma (e.g., traffic accident) was the main reason for admission in 11 of the patients. An acute cardiac disease (cardiac arrest) was the primary reason in two patients while 13 others had additional severe cardiac impairment in the course of another disease (e.g., myocardial infarction during surgery). Sepsis was present in 21 of the patients. Dialysis was necessary in 6. Respiratory aid was given to 47.

Mannitol was given to some patients in an attempt to reduce intracerebral edema (three patients), to maintain urinary output (one patient with cardiogenic shock), or to increase blood volume (in order to reduce the risk of developing renal failure in the course of extensive general surgery, as in eight patients with aortic aneurysm). A tetracosactoid test was performed in a total of 16 patients. A basal measurement of p-cortisol had been performed in ten of these patients before the test. Nine had an initial basal morning cortisol lower than 400 nmol/l. Six performed the tetracosactoid test as the initial test of adrenal function.

To determine whether adrenal insufficiency characterizes patients under stress we examined the proportion of various subgroups of patients who had p-cortisol levels lower than either 400 [15] or 500 nmol/l [16, 17, 18].

Methods

Samples of p-cortisol was drawn on days 1–24 between 7 and 8 a.m. The tetracosactoid test involved intravenous injection of 250 µg. Sampling for p-cortisol was carried out before injection and 30 and 60 min after injection. Analysis of p-cortisol was performed by radioimmunoassay (Immulite, DPC Diagnostic Products, Los Angeles, Calif., USA). None of the patients was on steroids before sampling of p-cortisol or during the tetracosactoid test. Severity was graded on the basis of the second edition of the Acute Physiology and Chronic Health Evaluation (APACHE II) [21] within 24 h after admission at the ICU. In 51 patients APACHE II scores were also calculated using data on the same day or close to it (if relevant data were missing) when the first sample for analysis of p-cortisol was drawn (files missing in four).

Statistics

Fisher’s exact test was used. Univariate and multivariate parametric linear regression analyses were performed. A two-tailed P value of less than 0.05 was considered significant. Relative risk (RR) and confidence interval (CI) for low p-cortisol were compared by Fisher’s exact test. This was performed in the patients with a p-cortisol below 400 and compared with those with a level of 400 nmol/l or higher. The same comparison was carried out in those with p-cortisol below 500 versus those whose level was 500 nmol/l or higher. When parametric analyses of mean values were calculated, data are also given as standard deviation and range. Linear regression analyses were used.

Results

Plasma and 24-h urinary cortisol

Samples were taken on day 3 (median) after admission to the ICU (mean 4.8 ± 4.7, range 1–24). The median concentration of basal p-cortisol was 550 nmol/l (mean 564 ± 357, range 20–1764). Twenty patients (36%) had a concentration lower than 400 nmol/l, and 26 (47%) had one lower than 500 nmol/l (Fig. 1). In some of these patients p-cortisol was sampled more than once (Fig. 2).

Twenty-four hour urinary cortisol excretion was analyzed in 34 patients. The median concentration was 912 nmol/24 h (mean 1701 ± 2288, range 96–9999). There was a positive correlation between basal p-cortisol levels and urinary cortisol concentration (r = 0.45, P = 0.009) and related to the 24-h urinary cortisol (r = 0.47, P = 0.006). There was no correlation between 24-h urinary cortisol and 24-h urinary volume.

The p-cortisol levels in men did not differ significantly from those in women. Values were below 400 nmol/l in 15 of 31 men vs. 5 of 21 women, and below 500 nmol/l in 20 men vs. 6 women (P = 0.051).