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# 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 laparatomy 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. Etomidate 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 adrenocorticotropic 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 ($P = 0.051$).

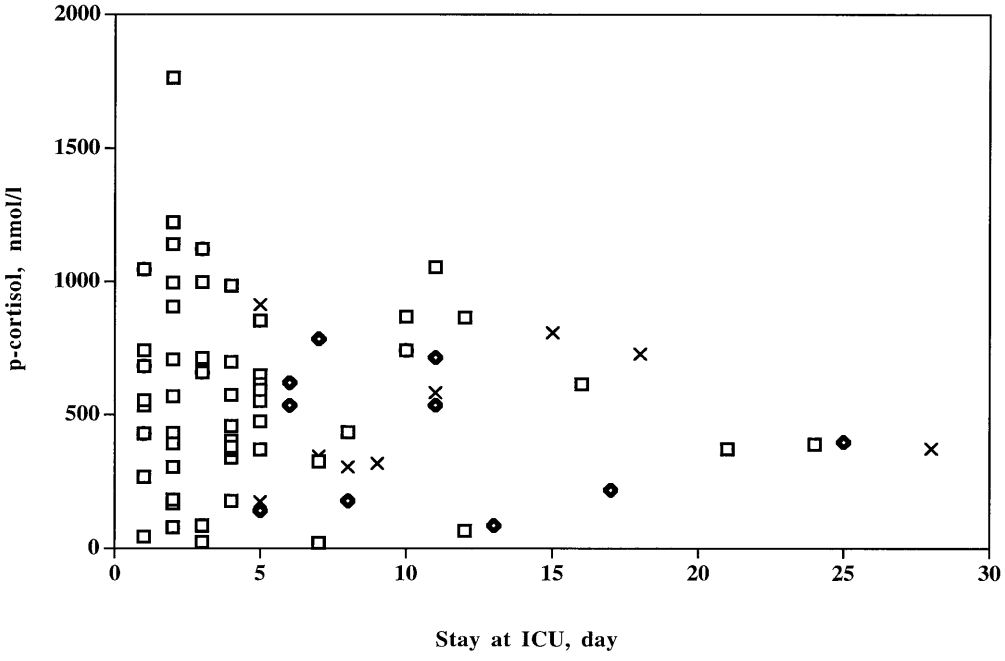


**Fig. 1** Distribution of p-cortisol during ICU stay in 55 patients. In patients with several samples: first sample (*squares*), second sample (*diamonds*), third sample (*X*)

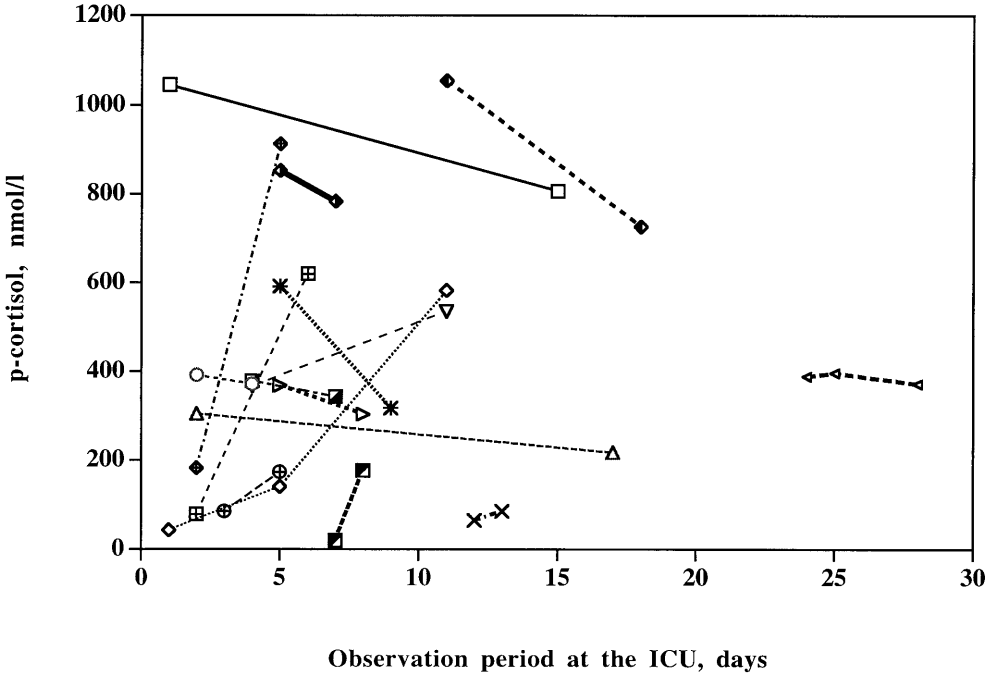


**Fig. 2** Individual change in p-cortisol during observation at the ICU, in patients with several samples drawn

The distribution of patients in regard to their p-cortisol and the relationship to various clinical and medical conditions are presented in Table 1. A p-cortisol level lower than 400 nmol/l was associated with patients who had been admitted due to trauma (8 of 11 patients, $P = 0.011$, RR 4.7, CI 1.4–15.6). This was also the case in those with p-cortisol level lower than 500 nmol/l (9 of 11, $P = 0.017$, RR 5.0, CI 1.2–21). Levels were below 400 nmol/l in patients with cerebral affection (11 of 20, $P = 0.043$, RR 2.1, CI 1.1–4.3) and in those requiring respiratory aid (19 of 45, $P = 0.040$, RR 1.3, CI 1.1–1.6).

Therapy with mannitol was associated with p-cortisol levels below 400 nmol/l (9 of 13, $P = 0.008$, RR 3.9, CI 1.4–11) and with those below 500 nmol/l (10 of 13,

**Table 1** Distribution of patients with various clinical conditions and plasma cortisol (nmol/l)

| Clinical condition, outcome and therapy | p- cortisol in nmol/l | | | | p for cortisol | |
|---|---|---|---|---|---|---|
| | < 400 n = 20 | < 500 n = 26 | ≥ 400 n = 35 | ≥ 500 n = 29 | < 400 | < 500 |
| Death | 3 | 3 | 5 | 5 | n.s. | n.s. |
| Need for dialysis | 2 | 2 | 4 | 4 | n.s. | n.s. |
| Sepsis | 10 | 11 | 11 | 10 | n.s. | n.s. |
| Surgery | 16 | 21 | 24 | 19 | n.s. | n.s. |
| – elective | 4 | 7 | 9 | 6 | n.s. | n.s. |
| – acute | 12 | 14 | 15 | 13 | n.s. | n.s. |
| – aortic aneurysm | 6 | 8 | 8 | 6 | n.s. | n.s. |
| Cardiac dysfunction, acute | 3 | 5 | 17 | 21 | n.s. | n.s. |
| ARDS | 6 | 7 | 5 | 4 | n.s. | n.s. |
| Cerebral trauma | 5 | 6 | 4 | 3 | n.s. | n.s. |
| Trauma not cerebral | 8 | 9 | 3 | 2 | 0.011 | 0.017 |
| Cerebral affection | 11 | 12 | 9 | 8 | 0.043 | n.s. |
| Respiratory aid | 20 | 24 | 27 | 23 | 0.041 | n.s. |
| Mannitol therapy | 9 | 10 | 4 | 3 | 0.008 | 0.025 |
| Inotropic therapy | 8 | 9 | 13 | 12 | n.s. | n.s. |
| Antibiotic therapy | 20 | 25 | 30 | 25 | n.s. | n.s. |
| Calcium antagonists | 7 | 7 | 5 | 5 | n.s. | n.s. |
| $\beta$ blocker therapy | 1 | 1 | 6 | 6 | n.s. | n.s. |
| Warfarin therapy | 3 | 3 | 5 | 5 | n.s. | n.s. |
| Heparin or LMWH | 6 | 8 | 16 | 14 | n.s. | n.s. |

LMWH = low molecular weight heparin

$P = 0.025$, RR 3.7, CI 1.1–12). Patients who received mannitol had significantly lower p-cortisol (326 nmol/l ± 269 versus 638 ± 352, $P = 0.005$). Lower p-cortisol was also found in those who suffered from trauma (269 ± 194 versus 638 ± 352, $P = 0.002$) or skull trauma (342 ± 305 versus 608 ± 354, $P = 0.040$) and in those who were on antibiotics (534 ± 326 versus 869 ± 543, $P = 0.044$).

## Tetracosactoid test

The tetracosactoid test was performed in 16 patients, at a median after 6 days at the ICU (mean 7.6 ± 6.5, range 1–25). These patients had a mean age of 57 ± 20.5 years (range 15–76). The median basal morning p-cortisol in these patients was 577 nmol/l (mean 554 ± 304, range 85–1121). Five (31 %) had a p-cortisol level lower than 400 nmol/l at baseline, and six (38 %, Fig. 3) had one lower than 500 nmol/l. An increase of less than 200 nmol/l at 30 min was found in nine (56 %) and at 60 min in four (25 %; see Fig. 3). Eleven had a p-cortisol level lower than 400 nmol/l at time 0 and/or a low increase at 30 min (69 %). Two had low p-cortisol but more than a 200 nmol/l increase in response to the tetracosactoid at 30 min. One of these patients had a cerebral trauma and the other a body trauma not involving the skull.

There was no correlation between initial p-cortisol and response to tetracosactoid at 30 min or at 60 min. In all but two patients the increase in p-cortisol was greater at 60 min than at 30 min (mean increase 314 ± 183 versus 244 ± 181 nmol/l, Student's paired $t$ test $P = 0.012$, Wilcoxon $P = 0.006$). There was a univariate correlation between p-cortisol and age ($r = 0.36$, $P = 0.006$). There was no correlation of p-cortisol to the duration from admittance to the ICU until sampling, or to tetracosactoid response at 30 or 60 min. When the 60-min values were considered, obtained during the tetracosactoid test, there was a significant inverse correlation between the APACHE II score and the rise in p-cortisol ($n = 12$, $r = –0.60$, $P = 0.041$). The APACHE II score at entry to the ICU was calculated in 46 of the patients and the mean was 15.7 ± 7.8 (range 2–35). There was no univariate correlation of APACHE II score to baseline p-cortisol or to the rise in p-cortisol at 30 min after tetracosactoid. There was also no correlation between p-cortisol and the current APACHE II scores ($n = 51$), calculated for the same day or the most possible day closest to the p-cortisol sampling ($R^2 = 0.00$, n.s.).

Multivariance analyses were performed with the p-cortisol as the dependent variable (predictability of p-cortisol). In one model the drugs used were included as independent variables (inotropics, antibiotics, beta-blockers, calcium antagonists, anticoagulants, acetyl salicylates, mannitol). The $R^2$ value for the overall model was 0.31 ($P = 0.011$). The drugs with a $P$ value less than 0.05 were mannitol ($P = 0.0098$) and antibiotics ($P = 0.0184$), both with an inverse correlation. In a stepwise model including only significant parameters the $R^2$ was 0.26, with a positive correlation to the use of inotro-

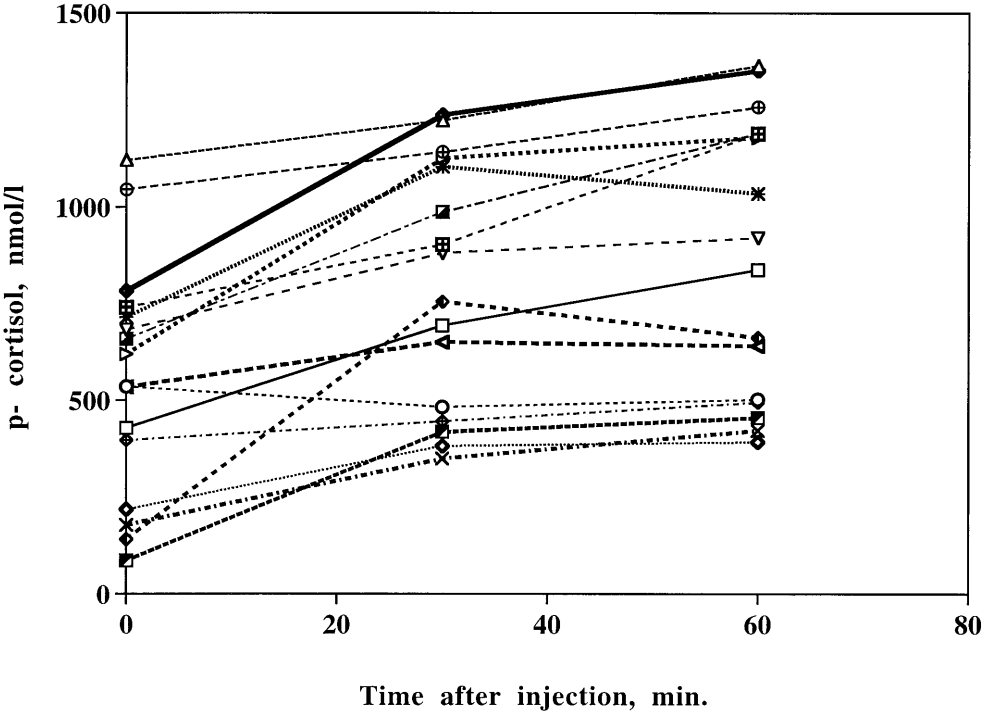


**Fig. 3** P-cortisol after tetracosactoid test in 16 patients. Individual distributions are given

pic drugs ($P = 0.0032$) and an inverse correlation to the use of antibiotics ($P = 0.038$) and mannitol ($P = 0.0012$). A model using clinical parameters as independent factors (elective or acute surgery, general trauma, cerebral trauma, aortic aneurysm, septicemia, cerebrovascular disease, adult respiratory distress syndrome, acute cardiac dysfunction, death, APACHE II score, need of respiratory aid, or dialysis) yielded an $R^2$ of 0.32 (n.s.). Stepwise analyses left general trauma as the only, inversely related, significant factor ($R^2 = 0.17$, $P = 0.0015$).

## Discussion

This study included several of the more urgent reasons for admission to an ICU; for example, 85 % of these patients needed respiratory aid and 91 % antibiotics. However, when interpreting these data, one must consider the differences in a patient population admitted to the ICU at different centers.

According to the various p-cortisol limits for patients under stress, as suggested for adrenal insufficiency, our calculations used two different limits: p-cortisol levels lower than either 400 [15] or 500 nmol/l [16, 17, 18]. Using these limits, we found that at least 36 % of the patients in our ICU had lowered p-cortisol. This is in agreement with some [4, 22, 23] but not with other studies [24, 25, 26]. Drucker et al. [24] found very high concentrations, with a mean of 1232 nmol/l. This is more than twice as high as our measurements. Notable is that in the study by Drucker et al. [24] the cortisol samples were drawn within 24 h after admission to the ICU. This difference could be due to either more stress at that early stage of the disease or a better ability of the adrenals to respond to stress initially than after a more prolonged time at the ICU, for example, when multiorgan dysfunction has progressed. Additionally, it is very difficult to determine the degree of stress at the time of blood sampling in these patients, most of them being under sedation. However, some had greatly increased p-cortisol levels. If these patients are considered to have a normal adrenal function with a physiological response, one would expect much higher values also in the others, for example, as seen by Drucker et al. [24]. The stress noted in these patients evidently did not differ from that in the overall group. Therefore a lowered p-cortisol, found in several of the patients in this study, may be due to impairment at various levels of the hypothalamic-hypophyseal-adrenal axis (HHA). Such dysfunction may be strengthened since the tetracosactoid test in this study showed a low response in up to two-thirds of those with low initial p-cortisol. This impaired response could thus be due to a relative dysfunction of the adrenal glands. Therefore the low basal p-cortisol in the other patients (those with a normal response to the tetracosactoid test) may have had a reduced function of the HHA. The latter is a possible explanation for the findings of significantly lower basal cortisol in patients who suffered from skull trauma. Some of the

patients had recovered their p-cortisol once the tetracosactoid test was performed, indicating an improvement in the adrenal function during the recovery period.

There was a total lack of correlation of basal cortisol with the APACHE II score, calculated at the time for sampling. This may be due to the fact either that the APACHE II score is not by itself a predictor of stress, or that the stress is equally extensive in "minor" and "major" traumata necessitating ICU care. It also is not a predictor of p-cortisol. Possibly even a "minor" ICU-necessitating trauma may cause optimal release of p-cortisol. Other sources of interference are also probable in the release of p-cortisol in addition to the HHA, such as local edema in the hormone-producing tissues.

Notably, patients treated with antibiotics had lower basal cortisol while those with defined sepsis did not. This difference could be due to fact that even a lower extent of bacterial infections (e.g., toxins, increase in cytokines) interferes with the endocrine system, or that the antibiotics induces such negative side effect by themselves.

The 24-h urinary cortisol excretion analyzed in 34 of the patients is of major interest because these data are lacking in the literature. The positive correlation between cortisol levels in p-cortisol and urinary cortisol secretion suggests that increased levels of cortisol are more the result of increased cortisol secretion than of decreased hepatic clearance in the patients under study. This suggests a functional integrity of the hypophyseal-adrenal axis in the majority of the patients. The limitations of this diagnostic approach is the presence of acute renal failure since in these patients a decrease in urinary cortisol may be due to a decreased glomerular clearance and lowered urinary output.

There was a significant association between low p-cortisol level and major trauma, cerebral affection, and the need for respiratory aid. Therefore especially such patients should be analyzed for p-cortisol to detect subnormal concentrations, in addition to other patients not responding to conventional therapy.

Patients on therapy with mannitol also had decreased p-cortisol. However, mannitol may be a confounding factor in patients with poor diuresis and possibly low blood pressure. Our data did not show a significant relationship for those on dialysis or on inotropics, nor a correlation to the urinary output of the patients. Thus mannitol per se may remain in the body and in some way alter the function of the HHA. Multivariance analysis revealed that patients on a combination of mannitol and antibiotics, but without inotropic drugs, seemed to have lower p-cortisol values. There was no such multivariance coupling to clinical data, except for those with generally greater trauma. It is notable, however, that mannitol treatment in patients with severe head injuries showed a possible nephrotoxic side effect [27]. We cannot exclude that similar adverse effects due to mannitol are also present on the adrenal glands. Further research is necessary to determine the significance of these findings.

The value of low-dose hydrocortisone therapy is established in septic shock patients, assuming the presence of a partly adrenal insufficiency [28]. Presently we consider supraphysiological doses of hydrocortisone in the situation when the patient cannot be stabilized with traditional treatment with volume replacement and inotropics, especially when p-cortisol or the tetracosactoid test indicates a reduced adrenal function. These data and those of others therefore indicate that there may be a benefit to substituting low-dose corticosteroids in patients with relative adrenal insufficiency.

In conclusion, this study shows that a considerable proportion of patients treated in the ICU may have a subnormal function of the HHA axis resulting in low p-cortisol levels. A more frequent measurement of baseline p-cortisol or after tetracosactoid may help to detect those patients at risk of HHA dysfunction.

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