Adrenal failure and high dose dexamethasone

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Abstract. Objective: To determine the effect of high dose dexamethasone (HDD) on adrenal function in critical illness. Setting and patients: ICU-patients with multiple organ dysfunction syndrome (MODS) admitted for emergency reasons were included. Interventions: Twenty-five patients, who received 100-mg dexamethasone on admission (DX+), were compared to 10 control patients (DX−). Measurements and main results: Baseline cortisol levels, incidence of baseline cortisol level <0.69 μmol/l and cortisol response >0.25 μmol/l after 250-μg corticotropin (adrenal response) on day four of intensive care treatment were measured. On day 4, 90-100% of patients had a baseline cortisol <0.69 μmol/l. On day four, 23/25 (92%) DX+ patients compared to 4/10 (40%) DX− patients had an adrenal response of >0.25 μmol/l (p=0.003). An adequate adrenal response was associated with decrease in dopamine need over four days (decrease 3.9 μg/kg/min) as opposed to an inadequate response (dopamine increase 1.2 μg/kg/min) (p=0.026).

Case-control analysis, in which the DX− patients were matched for APACHE II score and cortisol level on admission with DX+ patients, confirmed the cortisol results. It revealed a trend towards greater mean arterial pressures over four days in DX+ patients (+12.3 versus +2.5 mmHg, p=0.07).

Conclusions: Relative adrenal failure occurred in 90-100% of emergency patients with MODS within four days. HDD-treated patients had a better adrenal response. An adequate adrenal response was associated with the need for fewer vasopressors.

Introduction

Relative adrenal insufficiency (hereafter: adrenal insufficiency) is frequently found in critically ill patients, although it is not known at what point during the course of the illness that it occurs [1-8]. Treatment of adrenal failure in patients in septic shock with low dose corticosteroids is associated with improved outcome [2,6]. The administration of low dose corticosteroids aims to restore corticosteroid deficiency. Higher doses of steroids necessary to achieve modulation of the immune response were used in clinical practice in the 1980s. The anti-inflammatory properties of high dose corticosteroids were thought to have a potentially therapeutic benefit in severe sepsis [9]. These effects include; prevention of the activation of the complement cascade, inhibition of the inducible nitric oxide synthase, prevention of endotoxin-induced hyperaggregation and adhesion of leukocytes, decrease in platelet-activating factor during endotoxin challenge, prevention of tumour necrosis factor (TNF) and interleukin (IL)-1 release from mononuclear cells, and the prevention of prostaglandin generation through induction of phospholipase A2 inhibitor [9].

The benefit of high dose corticosteroids in sepsis however, remains controversial. In a meta-analysis, Cronin et al. describe a trend towards increased mortality in septic patients treated with high dose corticosteroids [9]. However, the study populations were heterogeneous [9,10], different types and dosages of corticosteroids were used for varying lengths of time and definitions of septic shock varied [11]. The studies were all published before 1993 and most were not of sufficient methodological quality [3]. It was suggested that some subgroups might benefit from high dose corticosteroid therapy, if initiated very early [3], as was demonstrated in specific entities like severe typhoid fever [12] or bacterial meningitis in children [13] and adults [14]. These beneficial effects are sufficient reason for some intensivists to treat both septic and patients with multi organ dysfunction a bolus of high dose dexamethasone (HDD) on admission, although sepsis guidelines discourage this [15].

It is common practice in our intensive care unit (ICU) to treat patients with multi organ dysfunction syndrome (MODS) with 100 mg HDD on admission. One of the intensivists, however, did not administer HDD during the study period. This allowed us to perform an observational study in order to determine the effect of HDD on cortisol levels and the incidence of adrenal failure. Additionally we performed a post-hoc case-control analysis to correct for confounding factors such as severity of disease.

Patients and methods

Patients

Patients with MODS admitted to the ICU as emergencies were included. MODS was defined as respiratory failure with the need for mechanical ventilation and failure of one or more other organ functions. Patients were excluded if they were admitted after uncomplicated elective surgery, were expected to stay less than 4 days in the ICU, had a prior history of adrenal insufficiency, had been administered together with other steroids, electrolytes were prescribed, or angiotensin-converting enzyme inhibitors were used for varying lengths of time and definitions of septic shock varied [11]. The studies were all published before 1993 and most were not of sufficient methodological quality [3]. It was suggested that some subgroups might benefit from high dose corticosteroid therapy, if initiated very early [3], as was demonstrated in specific entities like severe typhoid fever [12] or bacterial meningitis in children [13] and adults [14]. These beneficial effects are sufficient reason for some intensivists to treat both septic and patients with multi organ dysfunction a bolus of high dose dexamethasone (HDD) on admission, although sepsis guidelines discourage this [15].

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tered etomidate in the 48 hours before admission to the ICU or had previously taken corticosteroids. Inclusion was allowed if there was no death, discharge from the ICU or administration of corticosteroids or other medication known to interfere with adrenal function within the observation period of four days. This four day period was based on preliminary data, which demonstrated that adrenal insufficiency (baseline cortisol level < 0.69 µmol/l) develops in the course of the first four days of ICU-stay in patients with MODS [16]. Acute Physiology And Chronic Health Evaluation (APACHE) II score was calculated within 24 hours after admission to the ICU [17]. In addition, Sequential Organ Failure Assessment (SOFA) scores [18] were recorded daily during ICU stay. Length of stay (LOS), mortality in the ICU and hospital mortality were recorded. Haemodynamic parameters including day one and four lowest mean arterial pressure (MAP), highest dopamine and noradrenalin dosage and the change in the lowest MAP, highest dopamine and noradrenalin dose between day one and four were analysed.

Interventions

Patients, who were treated with HDD 100 mg within the first hour of intensive care stay after the first measurement of cortisol, were observed (DX+ group). In addition, patients not receiving HDD treatment (DX- group) were observed. These control patients were the consecutively admitted patients with MODS, when the investigating intensivist was on duty. None of the patients received corticosteroids, other than dexamethasone on admission in the DX+ group. Apart from the administration of HDD, the attending physicians on our ICU followed a uniform course of action in the management of the patients.

Case-control analysis

To analyse potential confounding of the results by the severity of disease, we performed a case-control analysis of the data. The patients in the DX- group were blindly matched for APACHE II score and admission serum cortisol level to patients in the DX+ group.

Measurements

An arterial blood sample was drawn for the measurement of the serum cortisol level on admission to the ICU. Day 1 was defined as the day of admission until 24:00 and was therefore of variable length. On day 4, blood for a baseline cortisol measurement was drawn at 06:00. Immediately thereafter 250-µg synthetic corticotropin (tetra-cosactide, Synacthen®, Novartis, Arnhem, The Netherlands) was injected intravenously and after 30 and 60 minutes blood samples were drawn for a serum cortisol measurement. Serum cortisol levels were measured by electrochemiluminescence immunoassay using the Roche Modular E170 (Roche GmbH, Mannheim Germany). To assess adrenal response, we analysed the largest change in cortisol after corticotropin stimulation. This was considered inadequate in the case of a corticotropin-stimulated increase in serum cortisol level < 0.25 µmol/l irrespective of the baseline serum cortisol level [1;2]. Adrenal insufficiency was defined as a baseline or random cortisol level < 0.69 µmol/l [4;5;19], this applied to the patients who had not received dexamethasone on admission. In addition, we analysed the change in cortisol level between admission and day four.

Statistical analysis

Values are expressed as mean and standard deviation (± SD). In cases of skewed distribution median and interquartile range (IQR) are shown. For reasons of clarity, figures express median and IQR.
were analysed using the Student’s T test, Fisher’s exact test, Mann-Whitney U test or Pearson correlation where appropriate. The decline in SOFA score within each group over a period of time was tested by Wilcoxon signed rank test. A two sided p value below 0.05 was considered statistically significant. The analyses were made with the SPSS package 12 (SPSS, Chicago, Ill., USA).

Results

Patient characteristics
Baseline characteristics are shown in Table 1. The SOFA scores did not decline significantly over 4 days, in either the DX+ group (p=0.11) or in the DX- group (p=0.37). There was no significant difference between the groups in LOS, ICU and hospital mortality.

Baseline Cortisol
The median baseline cortisol on admission was 1.09 µmol/l (IQR 0.60-1.40) in the DX+ and 0.571 µmol/l (IQR 0.39-0.98) in the DX- group (p=0.08) (Table 1, Figure 1). Baseline cortisol levels decreased in all individual patients in the first 4 days, with or without HDD. As a consequence, on day four, all 25 patients in the DX+ group and nine of the ten (90%) patients in the DX- group (p=0.28) had a baseline cortisol level < 0.69 µmol/l (Table 2), at least in the control group indicating adrenal failure according to one commonly used definition [4;5;19] in nearly all the patients.

The DX+ group had a significantly more pronounced decrease in baseline cortisol over the four days: median decrease 0.850 µmol/l (IQR 0.43-1.27 µmol/l) versus 0.290 µmol/l (IQR 0.05-0.51 µmol/l) in the control group (p=0.008). This resulted in a trend towards a lower baseline cortisol on day four in these patients (Figure1).

Adrenal response
Cortisol response to corticotropin stimulation was considered adequate with an increase of cortisol ≥ 0.25 µmol/l in 23 / 25 (92%) of the DX+ patients and in 4 / 10 (40%) of the DX- patients (p=0.003), indicating a sufficient adrenal response in the majority of DX+ patients in contrast with the control patients (Table 2). These DX+ patients more frequently had a baseline cortisol < 0.69 µmol/l on day four, suggesting a decrease in adrenal cortisol production due to secondary causes, for instance failure of the central nervous system (CNS)-hypothalamic-pituitary-adrenal (HPA) axis or corticotropin resistance [4;5].

Haemodynamic parameters
On day four we were unable to demonstrate a statistical difference between the two groups in haemodynamic parameters such as; lowest mean arterial pressure (MAP), highest dose of dopamine or highest dose of noradrenalin (Figures 2, 3 and 4). Neither was there a significant difference between the groups in the mean change in MAP (increase 6.5 mmHg [SD 17.0] in DX+ versus 2.5 mmHg [SD 10.8] in DX- , p=0.50), mean change in dopamine dose (decrease 1.0 µg/kg/min [SD 5.1] versus increase 2.1 µg/kg/min [SD 5.7], p=0.13) or median increase in noradrenalin dose (0.0 µg/kg/min [IQR 0.0-0.0] versus 0.0 µg/kg/min [IQR 0.0-2.5], p=0.12) in 4 days.

Case-control analysis
Mean APACHE II score and median admission cortisol levels of the 10 matched DX+ patients were comparable to the values of the 10 DX- patients shown in Table 1. Table 1 also shows the other baseline characteristics of these patients.

The results of the adrenal measurements of this case-control analysis are summarised in Figure 1 and Table 2 and are in essence the same as in the primary analysis.
Haemodynamic parameters and adrenal response

The patients with an inadequate adrenal response on day 4 had an increased need for dopamine (mean change in dose of +3.9 µg/kg/min (SD 4.6)) and noradrenalin (median change 0.0 µg/kg/min (IQR -0.5 – 0.0)) over the four day period. In contrast, the patients with an adequate adrenal response showed a decrease in the need of dopamine (mean change in dose of -2.4 µg/kg/min (SD 5.2)) (p=0.026) and noradrenalin (median change 0.0 µg/kg/min (IQR -0.5 – 0.0)) (p=0.018).

Haemodynamic parameters and baseline cortisol on day four

In our study, no correlation could be found between day four baseline cortisol level and haemodynamic parameters (lowest MAP, highest dose of dopamine or noradrenalin on day four and change in dopamine or noradrenalin levels after high dose steroids [20]). The induction of adrenal failure might be related to the increase in mortality in patients treated with HDD. It has previously been shown that 4-ng dexamethasone does not suppress cortisol levels [21]. A higher dose dexamethasone may override a potential resistance of the HPA-axis to the feedback of low dose dexamethasone and thus result in suppression of cortisol synthesis. On the other hand, preservation of adrenal function and response by HDD might result from modulation of the systemic inflammatory response syndrome (SIRS).

In contrast to the reports [9] on HDD being related to a trend towards a higher mortality, we did not find any difference in ICU or hospital mortality or LOS between the DX+ and control group. However, our study was not powered to demonstrate differences in mortality.

Baseline cortisol levels decrease in the first four days

We have shown that cortisol levels on admission are high and show decrease sharply during the first four days of ICU-treatment. This results in cortisol levels < 0.69 µmol/l, in most of the patients without HDD, suggesting adrenal failure – although without haemodynamic confirmation. The decrease in cortisol is not attributable to an improved condition, as there is no remarkable decrease in the SOFA score during these four days. As might be anticipated, all DX+ patients had a cortisol level < 0.69 µmol/l on the fourth day, its significance will be discussed later.

It is known that the incidence of adrenal failure in ICU patients with refractory septic shock is 50 - 75% [4,7]. Our data demonstrate that adrenal failure develops in the first four days of ICU treatment. Other reports on the onset of adrenal failure are scarce [22]. In our study, the incidence of baseline cortisol < 0.69 µmol/l (in 90% of control patients) on the fourth day of ICU stay in patients with MODS is remarkably higher than the aforementioned incidence [4,7].

Diagnosis of adrenal failure

To evaluate the entire CNS – HPA axis in severely stressed ICU-patients, random cortisol levels of 0.69 µmol/l could be used as a threshold value for an appropriate response to critical illness [4,5,23]. Levels below this value are associated with steroid-responsive hypotension [4]. For this reason, we used a baseline cortisol of < 0.69 µmol/l to...
indicate adrenal insufficiency in our patients. The diagnosis of adrenal insufficiency in critically ill patients is controversial, though. Various thresholds have been postulated [19,22,24] and it has been suggested there might not even be an absolute cortisol threshold for HPA-axis failure [7].

Further scientific data seems to support the concept of adrenal response. In a large group of septic shock patients a cortisol response of < 250 μmol/l to high dose corticotropin stimulation was associated with a higher mortality [1] and corticosteroid suppletion was beneficial to these patients [2]. More recently this benefit was seen to be confined to the patients with ARDS [25]. A drawback of this concept is, that it is not immediately apparent why reduced adrenal response despite high basal total cortisol, is predictive of responsiveness to hydrocortisone suppletion in septic shock [26].

Causes of adrenal failure

The most common cause of acute adrenal insufficiency in the ICU is sepsis and SIRS (4). Mediators released in sepsis play a role. Cytokines such as IL-1β, IL-6 and TNF-α can either stimulate or inhibit the synthesis, release and action of cortisol by influence on any level of the hypothalamic-pituitary-adrenal (HPA)-axis or on the glucocorticoid receptor [4,15]. The effects of HDD on mediator production and release could influence the adrenal function and HPA-axis in addition to the direct feedback of HDD on the HPA-axis. It remains speculation whether it was an effect of modulation of the cytokine profile by HDD, which resulted in a more preserved adrenal response in the DX+ patients. Though we could not demonstrate a statistically significant difference in haemodynamic improvement in this small study-population, the matched DX+ patients showed a trend towards a better increase in MAP compared to control patients. The patients with an adequate adrenal response showed a decline in their need for vasopressors unlike patients with an inadequate adrenal response. Most DX+ patients showed an adequate adrenal response. This suggests that HDD-treatment is beneficial to adrenal function, although the comparability of the two non-randomised groups is uncertain even after correction for APACHE II score and baseline cortisol.

Decrease in baseline cortisol and dexamethasone

In all patients baseline cortisol levels decreased in the first 4 days, but DX+ patients had a significantly more pronounced decrease. This might be a reflection of the poor comparability of the groups, although this decrease results in a trend towards lower baseline cortisol levels on day four in the DX+ patients.

Adrenal failure in septic shock can be further classified [5]. Primary adrenal failure is indicated by a low baseline cortisol concentration and an inadequate cortisol response following corticotropin stimulation. In CNS-HPA-axis failure, a low baseline cortisol concentration is accompanied by an adequate response following corticotropin infusions [23]. As 250-μg corticotropin is supraphysiological and can override adrenal resistance [4], low baseline cortisol concentration that increases with this high dose corticotropin might also signify corticotropin resistance [5].

The better adrenal response in the DX+ group may suggest that the more pronounced decrease in adrenal cortisol production on day four might be explained by CNS-HPA-axis failure or corticotropin resistance [5]. Another possibility is that dexamethasone has ongoing biological effects on the tissues on day four. Dexamethasone has an elimination half-life of 2.8 to 6.2 hours, but the half-life of the biological action is 36 to 72 hours [27]. Considering that the effect lasts at least two to three times as long as the biological half-life, it seems possible that after three days dexamethasone is sufficiently active in the tissues, though the concentration in the blood is not measurable (data of two patients which are not shown). In that case, there might be less need of endogenous cortisol production and consequently lower cortisol levels are measured. Whether this is the case remains uncertain, as we did not confirm adrenal insufficiency with the occurrence of haemodynamic improvement after administration of steroids [21]. However, the trend towards better increase in MAP after HDD in the case-control analysis without a change in vasopressor levels, although cortisol levels were low, is an argument in favour of less need of endogenous cortisol production on day 4 after HDD treatment. This was supported by the fact that more DX+ patients had an adequate adrenal response, and, that an adequate adrenal response (despite low baseline cortisol levels) was associated with a decrease in vasopressor need.

According to the sepsis guidelines [15], low dose steroids are recommended in septic shock patients. Up to May 2005, when the study was performed, these guidelines had not yet been fully implemented and therefore the control patients did not receive steroids in the observation period. After the four-day study period, the patients were treated for adrenal insufficiency according their response to the corticotropin stimulation test.

Limitations

Our study has potential drawbacks. First, we used random total cortisol levels in stead of free cortisol measurements for several reasons. In critically ill patients there is a decrease in cortisol binding globulin with an increase in the physiologically active free fraction of cortisol [4,7,26,28]. Hamrahian et al. described lower-than-expected levels of total cortisol in 39% of critically ill patients, while free cortisol levels were consistently elevated [29]. Though severity of sepsis is more closely related to an increase in free cortisol than in total cortisol [26], it remains a matter for speculation whether baseline free cortisol concentrations correlate better with outcomes [26,29]. The increment in total cortisol after corticotropin stimulation testing, adequately reflects the increase in free cortisol [26]. Instead of measuring free cortisol or correcting for serum albumin level, we therefore used the better established thresholds for total cortisol concentrations.

Secondly, we did not measure corticotropin levels in our patients, because of the limited additional diagnostic value under these circum-

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Table 2. Number of patients with (DX+) and without (DX-) HDD with inadequate baseline cortisol levels and cortisol response. DX+ patients in the case-control analyses are denoted by DX*+ and P*.

<table>
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<th>DX+ (N=25)</th>
<th>DX- (N=10)</th>
<th>P</th>
<th>DX*+ (N=10)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 baseline cortisol &lt; 0.69 μmol/l</td>
<td>7/25 (28%)</td>
<td>6/10 (60%)</td>
<td>0.12</td>
<td>6/10 (60%)</td>
<td>1.00</td>
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<tr>
<td>Day 4 baseline cortisol &lt; 0.69 μmol/l</td>
<td>25/25 (100%)</td>
<td>9/10 (90%)</td>
<td>0.28</td>
<td>10/10 (100%)</td>
<td>1.00</td>
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<tr>
<td>Day 4 rise in cortisol &lt; 0.25 μmol/l after corticotropin stimulation</td>
<td>2/25 (8%)</td>
<td>6/10 (60%)</td>
<td>0.003</td>
<td>0/10 (0%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Day 4 baseline cortisol &lt; 0.69 μmol/l with rise &gt; 0.25 μmol/l after corticotropin stimulation</td>
<td>4/10 (40%)</td>
<td>0.003</td>
<td>10/10 (100%)</td>
<td>0.011</td>
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stances. Sepsis may interfere with both adrenal cortisol production and hypothalamic-pituitary dysfunction (23); low cortisol levels can be accompanied by an elevated as well as a non-elevated cortisol-to-creatinine ratio. Moreover, decreased cortisol levels do not distinguish between secondary adrenal failure and lesser need of adrenal cortisol production.

The main limitation is the observational and non-randomised design of the study. The International Sepsis Guidelines discourage the use of HSD (15). This limited the randomisation, despite the benefits of HSD on the modulation of the immune response. The use of HSD by individual intensivists was therefore, a more acceptable way to collect data. This led to a selection of patients, which is shown by differences in APACHE II score and baseline cortisol. We believe that the selection primarily concerned the severity of disease, as apart from the administration of HSD, the management by the individual physicians in our ICU was uniform. To reduce the impact of the selection by severity of disease, we performed a case-control analysis which controlled for APACHE score and baseline cortisol level. The case-control analysis confirmed the more marked decrease in cortisol levels and the significantly better adrenal response in the DX+ patients. This analysis revealed a trend towards a better haemodynamic profile on day four after HSD treatment.

Because patients were included at day four, data about discharge or death in the first 3 days of ICU-stay are lacking. Because of exclusion of these short-stay patients, the effect of HSD on recovery or mortality is unknown and no conclusions can be drawn on the clinical usefulness of administration of HSD on admission.

**Clinical relevance**

Despite all the drawbacks in the design of the study, our data show that adrenal insufficiency develops in a very high proportion of critically ill patients over the course of days of ICU-stay. Although the non-randomised design limits the extrapolation of our results, this study suggests that HSD might preserve adrenal response in critically ill patients, at least on day four of ICU-stay. We can hypothesise, as haemodynamic parameters in our patients did not worsen, that on the fourth day after treatment with HSD the DX+ patients might not be adrenal insufficient in contrast with control patients, despite the low cortisol levels after HSD treatment. No conclusions can be based on our data about the overall clinical usefulness of HSD on admission by lack of data of short-stay patients and limited comparability of the groups. Because of the non-randomised study design, the current results can only be a guide for randomised studies to the clinical effects of HSD in critically ill patients.

**Conclusion**

Ninety percent of emergency ICU-patients with MODS, not treated with dexamethasone, developed relative adrenal insufficiency defined as a baseline cortisol < 0.69 μmol/l within four days.

In this non-randomised study, baseline cortisol levels decreased more in those patients who were treated with high dose dexamethasone on admission. At the same time, case-control analysis showed a trend towards a better haemodynamic profile in these patients.

We hypothesise that high dose dexamethasone might preserve adrenal response; this response seems to be associated with a decrease in the need for vasopressors.

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**References**


