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INTRODUCTION

The adrenal gland is an important endocrine organ, which supports the human organism's ability to react to factors threatening the integrity of the body either acutely or in a chronic-adaptive manner. As part of the stress response, the central nervous system (CNS) induces an activation of both the sympatho-adrenergic system by release of catecholamines, and the hypothalamic-pituitary (HPA) axis by release of steroid hormones (gluco- and mineralocorticoids), with the target to maintain homeostasis by influencing metabolic, cardiovascular, immunological, and endocrine functions. In this context, the adrenal gland plays the key role combining the location for synthesis and expression of catecholamines, glucocorticoids (GC), as well as of androgenic hormones and components of the renin-angiotensin-aldosterone (RAA) system.

Acute and chronic inflammatory diseases stimulate the HPA axis via the immune system, thereby leading to morphological and functional changes, especially of the adrenal cortex. This phenomenon has been described for acute infectious diseases, as well as for severe sepsis and septic shock. In patients with septic shock, however, the negative results of trials with high doses of glucocorticoids have evoked scepticism about their use over the years. Now, that there have been positive results for studies, using low doses of corticosteroids in patients with septic shock, the trend has swung in the opposite direction. There is still controversy over which patients profit most from this therapy, and also how to define and evaluate adrenal gland disorders.

PHYSIOLOGY OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The adrenal glands are part of a complex system that produces interacting hormones to maintain physiological integrity, especially during stress response [1]. This system named the hypothalamic-pituitary-adrenal (HPA) axis consists of the hypothalamic region that produces corticotropin-releasing hormone (CRH), triggering the pituitary gland. The anterior pituitary gland secretes corticotropin (ACTH) under stimulation from hypothalamic CRH. ACTH, in turn, stimulates the synthesis and release of glucocorticoids, mineralocorticoids, and androgenic steroids from the adrenal gland.

The HPA axis is stimulated not only by physical or psychological stress, but also by peptides like ADH and cytokines. Thus, the HPA axis plays an important role during infections and immunological disorders [2]. The HPA axis is probably the most important component of the stress response. due to its interaction with; the renin-angiotensin aldosterone system (RAAS) which regulates fluid and salt balance, synthesis of androgens (e.g., dehydro-epiandrosterone) with a possible impact on immunomodulation, and the sympatho-adrenergic system. Stimulation of the immune system by infections induces the release of proinflammatory cytokines like tumor necrosis factor-alpha (TNF- α), interleukin (IL)-1 β , or IL-6. These cytokines stimulate both the hypothalamus and the anterior pituitary gland, which finally leads to the release of glucocorticoids. IL-6 is also able to induce steroid release directly from the adrenal gland. In acute infections, this release maintains the metabolic and energy integrity. If the process becomes chronic, the HPA axis develops an adaptation, which induces the typical clinical manifestations such as hypercatabolic states, hyperglycemia, and the suppression of androgens, growth and thyroid hormones. These changes, however, may increase the risk of secondary infection. The increased cortisol levels suppress the higher regulatory levels of the HPA axis in terms of a negative feed-back loop. Hence, after major surgery, or during sepsis and septic shock, high cortisol and low ACTH levels are detectable. Even the infusion of dexamethasone or CRH is not able to suppress increased cortisol levels in these patients [3]. This phenomenon leads to the question how the cortisol release is induced. Several investigators have demonstrated that cortisol synthesis in critically ill patients is not regulated by ACTH, but by paracrine pathways via endothelin, atrial natriuretic peptide (ANP), or cytokines like IL-6 [4]. IL-6 directly induces the adrenal cortex to release cortisol, which when prolonged, can worsen the prognosis.

RELATIVE ADRENAL INSUFFICIENCY

The “classical” forms of adrenal insufficiency, which lead to an absolute deficiency of steroids, are rare in critically ill patients (0-3%) [5]. Instead they are characterized by morphological changes of the HPA axis. To reflect the notion that subnormal adrenal corticosteroid production during acute severe illness can occur without obvious structural defects in the HPA axis, deficiency syndromes due to a dysregulation have been termed “functional adrenal insufficiency” [6]. Functional adrenal insufficiency can develop during the course of an illness and is usually transient [7]. Decreased levels of glucocorticoids are seen much more often in the critically ill, which might be sufficient in normal subjects but are too low for stress situations due to a higher need. This led to the concept of “relative adrenal insufficiency” (RAI). The major cause of RAI is an inadequate synthesis of cortisol due to cellular dysfunction. Hence, in contrast to absolute adrenal insufficiency, the morphological changes in RAI may be minor, sometimes being characterized by cellular hyperplasia within the adrenal cortex. This is often combined with a peripheral glucocorticoid resistance of the target cells, which is caused by inflammatory events and aggravates the clinical course, although the absolute cortisol serum levels might be normal [8].

In septic shock, RAI may be due to impaired pituitary corticotropin release, attenuated adrenal response to corticotropin, and reduced cortisol synthesis [7]. In addition, cortisol transport capacity to effect sites may be reduced and response to cortisol may be impaired at the tissue level by cytokines modulating glucocorticoid receptor affinity to cortisol and/or glucocorticoid response elements [9]. In clinical trials, it has been demonstrated that prolonged treatment of systemic inflammation in patients with severe acute respiratory distress syndrome (ARDS) with methylprednisolone is able to improve the decreased glucocorticoid (GC) response by increasing the GC receptor affinity and reducing the NF- κ B-mediated DNA binding and transcription of proinflammatory cytokines [10]. Thus, if RAI can be identified, treatment with supplemental corticosteroids may be of benefit [7]. Prevalence of RAI in the critically ill varied from 0 to 77% with different definitions, cut point values, study populations, and adrenal function tests, and may be as high as 50-75 % in severe septic shock [7,11].

EVALUATION OF ADRENAL INSUFFICIENCY

In critically ill patients, primary causes of absolute or relative adrenal insufficiency are multiple and often not detectable, if no specific hypothesis exists. Volume-resistant septic shock or any other form of life-threatening hypotension with increasing need for catecholamines and no reasonable explanation should give reason to evaluate adrenal function. Formerly, a serum level cortisol value $<20 \mu\text{g/dl}$ was suggestive of the diagnosis. It is acknowledged that several factors complicate investigations of the HPA axis in patients with critical illness. Whenever available, a short-term ACTH stimulation test should be performed in all critically ill patients suspected of having adrenal insufficiency. In most patients, relative adrenal insufficiency (RAI) will be present, especially in patients with severe sepsis and septic shock. A clear definition of RAI, however, is still missing, and the pathophysiology is rather complex, which makes it difficult to define clear cut-offs for both basal serum cortisol concentrations and incremental increases after short-term ACTH stimulation tests. By considering free cortisol or the increase in free cortisol in response to ACTH we may be able to increase the accuracy of adrenocortical function tests [9]. Furthermore, extrapolating the diagnosis from reference values obtained from healthy people or patients with hypothalamic-pituitary-adrenal disorders may be misleading, since normal or high normal cortisol concentrations in septic shock may indicate inadequate adrenal response to stress. In a large series of patients, receiver operating characteristic curve (ROC) analysis reached highest sensitivity (68%) and specificity (65%) for the reference value $< 9 \mu\text{g/dl}$ (incremental increase) to detect non-responders [11]. A basal cortisol of $34 \mu\text{g/dl}$ and an incremental increase of $9 \mu\text{g/dl}$ after stimulation were the best cut-off points to discriminate between survivors and non-survivors. The higher the basal plasma cortisol and the weaker the cortisol response to corticotropin, the higher was the risk of death.

GLUCOCORTICOID REPLACEMENT IN PATIENTS WITH SEPTIC SHOCK

In patients with severe sepsis and septic shock, the individual clinical course is variable. The impact of the primary disease, as well as immunological factors (cytokines) affects the HPA axis, and functional testing is difficult. In contrast to the early phase of septic shock, adrenal cortisol release may recover, thus leading to relative adrenal insufficiency (RAI) with absolute steroid levels around or even above normal range. In refractory septic shock, prevalence of RAI may be as high as 50-75% [11]. Furthermore, dynamic testing is not always available in intensive care units, which makes it difficult for the physician considering hormone replacement therapy, because decisions have to be made within hours in severe forms of septic shock in order to improve prognosis.

The rationale for the use of high dose glucocorticoids in infection, sepsis, and shock can be attributed to well defined anti-inflammatory and haemodynamic effects which have been recognized for decades. Proposed mechanisms of protection include improvement of haemodynamic, metabolic, endocrine, and phagocytic functions, resulting in the maintenance of normal function of tissues including brain, liver, heart, kidneys, and adrenals. In addition, glucocorticoids are recognized to inhibit key features of inflammation: endothelial cell activation and damage, capillary leakage, granulocyte activation, adhesion and aggregation, complement activation, formation and release of eicosanoid metabolites, oxygen radicals, and lysosomal enzymes [12].

One long-term prospective study in humans looked at 179 bacteraemic septic shock patients over a period of eight years, using high doses of methylprednisolone (30-60 mg/kg) or dexamethasone (2-4 mg/kg) and showed a reduction in mortality from 38% to 10% [13]. Another study gave evidence that prolongation of treatment may be beneficial, since shock reversal and improved survival occurred after bolus glucocorticoid treatment early in the course of the illness but the benefit vanishes after several days [14]. Two meta-analyses of patients with severe sepsis and septic shock, who received up to 42 g hydrocortisone equivalent or more, concluded that high-doses of corticosteroids were ineffective [15] or harmful [16]. This was confirmed by a large randomized trial in 1987 [17]. Patients with proven gram-negative infections probably profited more from glucocorticoids [15]. In one analysis, studies with highest quality showed a worse outcome for corticosteroids. High dose glucocorticoids were associated with an increased risk of secondary infection, higher mortality, and increased incidence of renal and hepatic dysfunction [16]. Overall, high-dose glucocorticoids have failed to be effective in septic shock most probably due to suppression of the immune system.

Several randomized controlled trials with low dose corticosteroids in patients with septic shock have shown shock reversal and reduction of vasopressor support within a few days of the initiation of therapy in most patients [18-20]. In a cross-over study, mean arterial pressure and systemic vascular resistance increased during low dose hydrocortisone treatment, and heart rate, cardiac index, and norepinephrine requirement decreased significantly [21]. All effects were reversible with cessation of hydrocortisone. Some studies indicate that corticosteroid-induced increase of sensitivity to norepinephrine is more pronounced in patients with RAI than in patients without RAI [22]. There are multiple potential mechanisms by which corticosteroids may modulate vascular tone. There is considerable evidence that cytokine-induced formation of nitric oxide (NO) plays a central role in vasodilatation, catecholamine resistance, maldistribution of blood flow, mitochondrial and organ dysfunction, and that the amount of NO production correlates with shock severity and outcome [23]. In the aforementioned cross-over trial, norepinephrine requirement could be reduced by low dose hydrocortisone in nearly all patients within 1-2 days. Hydrocortisone treatment also induced a significant and prolonged decline of nitrite/nitrate levels, which significantly correlated with reduction of norepinephrine requirement during hydrocortisone infusion [21]. Considering the complex genomic and non-genomic actions of corticosteroids described above, it is probable that NO is not the only target. However, inhibition of NO synthesis by hydrocortisone at least contributes to shock reversal.

It is recognized that glucocorticoids modulate the stress response in a very complex manner, which includes not only anti-inflammatory and immunosuppressive actions to protect the host from overwhelming inflammation, but also immune enhancing effects. The final effect of corticosteroids may be dependent on multiple factors such as the dose, type of cell or tissue, time point of action, and the balance of pro- and anti-inflammatory cofactors. In summary, hydrocortisone significantly attenuated the inflammatory and anti-inflammatory response, granulocyte, monocytes, and endothelial activation. Monocyte HLA-DR expression was depressed, but receptor down regulation was limited and followed by a rebound increase after drug withdrawal [21]. In conclusion, the immune effects of low dose hydrocortisone treatment in septic shock may be characterized as immunomodulatory rather than immunosuppressive. Attenuation of a broad spectrum of the inflammatory response without causing severe immunosuppression might be a promising therapeutic approach, which goes far beyond haemodynamic stabilisation.

Although data on outcome in septic shock patients after low dose corticosteroid treatment is limited, up to 300 mg hydrocortisone per day appears to improve survival. In most trials with low dose corticosteroids [18-20], 28-day all cause mortality is reduced, whereas in high dose corticosteroid trials there was no significant effect. In a multicentre trial involving 300 patients with severe volume and catecholamine refractory septic shock, survival time was significantly increased in patients with RAI, but not in responders to ACTH [20]. Similar results were obtained for ICU and hospital mortality, but not for 1-year follow-up.

Significant increases in serious adverse events during treatment with low dose hydrocortisone have not been reported. The incidence of gastrointestinal bleeding, super-infections, or hyperglycemia has not been different in patients treated with corticosteroids or placebo, and wound infections were even less frequent in patients treated with low dose hydrocortisone [20]. Treatment with low dose hydrocortisone may induce an increase of sodium levels within a few days, and hypernatraemia with values > 155 mmol/l have been reported during prolonged treatment [19]. Nevertheless, the indications for low dose corticosteroids should be weighed against possible risks, and treatment should be limited to the shortest possible duration.

The dose of hydrocortisone in septic shock is similar to that for an adrenal crisis (100 mg initial bolus, followed by 200 to 300 mg per day), and the dose should be tapered when the patient stabilizes. Hydrocortisone should be preferred, although a comparative study of different corticosteroids has not been performed in septic shock, since most experience of low dose corticosteroid treatment in septic shock is derived from studies using hydrocortisone (see above). Furthermore, hydrocortisone is the synthetic equivalent of physiologically active compound cortisol, thus treatment with hydrocortisone directly replaces cortisol independently of the need for metabolic transformation. Hydrocortisone in contrast to dexamethasone has intrinsic mineralocorticoid activity. Fludrocortisone supplementation may be more indicated when glucocorticoids without mineralocorticoid activity are used.

It has not been established whether a weight adjusted regime (e.g., 0.18 mg/kg/h) [24] is superior to a fixed regime; moreover, a comparative study of bolus versus infusion regimes has not been performed so far. Patients should be weaned from low dose hydrocortisone over several days to avoid haemodynamic and immunologic rebound effects. In patients with septic shock, abrupt cessation of low dose hydrocortisone was followed by significant reversal of many haemodynamic and immunologic effects observed during corticosteroid therapy, even after a short treatment period of three days [21].

Adrenal function tests with 250 µg ACTH can be performed in patients with septic shock, however, at present it can not be recommended to exclude responders or patients with high random cortisol values from low dose corticosteroid therapy [7]. When basal serum cortisol concentrations are <15 µg/dl in septic shock, low dose hydrocortisone replacement is recommended, levels of >34 µg/dl are considered as sufficient. Between 15 and 34 µg/dl, an incremental increase of <9 µg/dl serum cortisol makes relative adrenal insufficiency likely, and therapy may be considered according to the clinical state [7]. The routine use of the low ACTH stimulation test (1 µg ACTH) can not be recommended at present until further data from well designed randomized studies in septic shock patients are available.

Most importantly, it has to be realized that all the aforementioned studies were performed in patients with catecholamine-resistant septic shock. So far there are no data justifying the use of low dose steroids in patients with sepsis and severe sepsis! Significant effects on outcome have been observed only in patients with systolic blood pressure < 90 mmHg despite vasopressor therapy [20]. It is not known yet if low dose corticosteroids are also effective in patients with less severe shock. Finally, sufficient data on the dose response characteristics of GCs in septic patients is still missing, and the so far recommended strategy using 200-300 mg hydrocortisone per day is based on empirical studies, and further investigations is needed.

CONCLUSIONS

Underproduction of adrenal hormones can lead to serious illness. Glucocorticoids play a critical permissive role in intermediary metabolism, are counter-regulatory in relation to insulin, modulate inflammatory and immune responses, and optimize cardiovascular and central nervous system function. Therefore, diseases leading to primary or secondary adrenal insufficiency may have severe sequelae, which often are life-threatening. The concept of relative adrenal insufficiency in critically ill patients with functional disorders of the hypothalamic-pituitary-adrenal axis has gained increasing attention over the last few years. For patients with severe sepsis and septic shock, treatment of this phenomenon is expected to have a major impact on the severity of illness and the prognosis. Both absolute and relative adrenal insufficiency should be diagnosed by using adequate laboratory investigations. In most cases, testing the basal level of cortisol combined with a short-term stimulation test with 250 µg ACTH is able to identify the problem. In Patients with critical illnesses, however, it continues to be difficult to diagnose relative adrenal insufficiency.

In cases of severe, volume- and catecholamine-resistant shock where there is suspicion of an adrenal crisis, immediate replacement therapy is indicated. Once the diagnosis is made, hydrocortisone is the preferred drug since it has both gluco- and mineralocorticoid effects. After stabilization, the patient's dose of glucocorticoids should be tapered down to a total of 20 to 35 mg hydrocortisone per day or equivalent analogues. Timing, dosage, and duration of glucocorticoid administration were adapted to different disease pathophysiological models and had major impact on outcome. Randomized controlled high-dose glucocorticoid trials failed to improve outcome, leading to scepticism against and avoidance of any glucocorticoids in septic patients by most ICU physicians over years, with exception of some special indications. However, recent randomized controlled trials with low doses of hydrocortisone in septic shock evoked a corticosteroid renaissance. Based on current data, an incremental increase of $< 9 \mu\text{g/dl}$ after a $250 \mu\text{g}$ ACTH stimulation test may be used in patients with severe septic shock to determine relative adrenal insufficiency. Meanwhile, prolonged treatment of septic shock with low doses of corticosteroids is considered as a therapeutic option to promote shock reversal and to increase vascular sensitivity to vasopressors.

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