Intensive Care Med (2000) 26: 1747–1755
DOI 10.1007/s001340000685

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Plasma cortisol levels before and during "low-dose" hydrocortisone therapy and their relationship to hemodynamic improvement in patients with septic shock

Received: 21 December 1999
Final revision received: 15 August 2000
Accepted: 21 August 2000
Published online: 18 November 2000

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Abstract *Objectives:* To compare cortisol levels during "low-dose" hydrocortisone therapy to basal and ACTH-stimulated endogenous levels and to assess whether clinical course and the need for catecholamines depend on cortisol levels and/or pretreatment adrenocortical responsiveness.
Design and setting: Prospective observational study in a medical ICU of a university hospital.
Patients: Twenty consecutive patients with septic shock and a cardiac index of 3.5 l/min or higher, started on "low-dose" hydrocortisone therapy (100 mg bolus, 10 mg/h for 7 days and subsequent tapering) within 72 h of the onset of shock.
Measurements and results: Basal total and free plasma cortisol levels ranged from 203 to 2169 and from 17 to 372 nmol/l. In 11 patients cortisol production was considered "inadequate" because there was neither a response to ACTH of at least 200 nmol/l nor a baseline level of at least 1000 nmol/l. Following the initiation of hydrocortisone therapy total and free cortisol levels increased 4.2- and 8.5-fold to median levels of 3587 (interquartile range 2679–5220) and 1210 (interquartile range 750–1846) nmol/l on day 1, and thereafter declined to median levels of 1310 nmol/l and 345 nmol/l on day 7. Patients with "inadequate" steroid production could be weaned from vasopressor therapy significantly faster, although their plasma free cortisol concentrations during the hydrocortisone treatment period did not differ.
Conclusions: (a) During proposed regimens of "low-dose" hydrocortisone therapy, initially achieved plasma cortisol concentrations considerably exceed basal and ACTH stimulated levels. (b) Cortisol concentrations decline subsequently, despite continuous application of a constant dose. (c) "Inadequate" endogenous steroid production appears to sensitize patients to the hemodynamic effects of a "therapeutic rise" in plasma cortisol levels.

Key words Shock · Sepsis · Septic shock · Cortisol · Adrenocorticotropic hormone · Hydrocortisone

Introduction

Despite improvement in several aspects of supportive care septic shock is still associated with mortality rates above 50 % [1, 2]. Although many aspects of its pathogenesis remain poorly understood, septic shock is thought to reflect a global endothelial inflammation that results from an imbalance between pro- and anti-inflammatory mechanisms.

Glucocorticoids have potent anti-inflammatory effects, are thought to maintain endothelial integrity, and may protect the host against overshooting defense reactions. Several lines of evidence suggest that these effects can be relevant for patients with severe sepsis. Acute

adrenal insufficiency per se can lead to a high output circulatory failure that resembles septic shock [3]. In addition, animal experiments [4] and clinical observations [5, 6, 7, 8] have shown that diminished steroid levels during sepsis are associated with adverse prognosis. In experimental settings in humans the administration of hydrocortisone before or during endotoxin challenge significantly reduces the inflammatory response [9]. On the other hand, some studies have shown that mortality is higher with increased levels of cortisol in patients with sepsis and septic shock [10, 11]. A recent prospective cohort study in 189 patients with septic shock found that patients with high cortisol levels and a reduced response to adrenocorticotropic hormone (ACTH, corticotropin) have the worst outcome [12].

Several attempts to improve the outcome of septic patients with high doses of steroids (approx. 2–8 g methylprednisolone in 24 h) have failed [13, 14, 15, 16, 17]. One meta-analysis concluded that steroids at such doses may even be harmful since they appear to increase the mortality in patients with overwhelming infection [16].

In contrast, two open studies [18, 19] and two recent randomized controlled trials [20, 21] have shown "low-dose" steroid therapy to have beneficial effects on hemodynamics and outcome in patients with septic shock, using no more than 300 mg hydrocortisone daily administered either as bolus injections of 100 mg three times daily or as continuous infusion. This work greatly stimulated the interest in using corticosteroids for septic patients, but little is known about the cortisol concentrations achieved by such a "low-dose" regimen and their relationship to endogenous basal and ACTH-induced cortisol levels. In fact, a number of studies have considered similar moderate amounts of hydrocortisone as a "supraphysiological" [18, 20], a "physiological" [19], a "replacement" [22], or a "stress" dose [21].

Moreover, it remains uncertain whether the response to hydrocortisone depends on endogenous steroid secretion. While some investigators believe that hemodynamic improvement after moderate doses of hydrocortisone detects adrenal insufficiency [18], a recent randomized trial by Bollaert et al. [20] suggested that the effectiveness of hydrocortisone is unrelated to adrenocortical function.

To obtain further insight into the pharmacological and pathophysiological basis of the proposed "low-dose" steroid treatment in septic patients we performed a prospective observational study in 20 medical intensive care patients with septic shock receiving continuous hydrocortisone therapy (10 mg/h). Total and free cortisol levels were determined under basal conditions, after ACTH stimulation, and during the subsequent course of hydrocortisone therapy to compare the levels under therapy with the endogenous production and to assess whether clinical course and hemodynamic response differ in patients with and without "inadequate" endogenous production.

Patients and methods

Patients

Adult patients with septic shock were included who were being treated in the medical intensive care unit of the Virchow Klinikum. Demographic data, the focus of sepsis, and causative organisms are presented in Table 1. According to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Committee [1] septic shock was defined as sepsis with hypotension of 90 mmHg or less or a drop of 40 mmHg or more despite adequate fluid resuscitation along with the presence of perfusion abnormalities. Furthermore, patients were only included with evidence of a causative organism or focus of infection and a cardiac index 3.5 l min^{-1} m^{-2} or greater. Patients with pancreatitis, infection with human immunodeficiency virus, and those in whom withholding maximal therapy was considered were excluded. Informed consent was obtained from next of kin.

Protocol

All patients were monitored hemodynamically with an arterial, a central venous, and a Swan-Ganz pulmonary artery catheter. After inclusion in the study dopamine, when given in daily doses above 240 mg, was switched to noradrenaline and dobutamine when possible depending on cardiac output and peripheral vascular resistance in order to make the needed doses of vasopressors comparable. Tapering of catecholamines and fluid expansion was guided by hemodynamic and pulmonary function to optimize tissue perfusion and gas exchange. Vasopressor therapy was usually titrated to achieve a mean arterial pressure of 70 mmHg or higher and a cardiac index of 3 l min^{-1} m^{-2}. The pulmonary artery occlusion pressure was aimed to be between 15 and 18 mmHg.

Within 72 h following the onset of septic shock a "short" corticotropin test was performed in all patients [23, 24]. For this plasma samples were drawn before and 30 min after the administration of 0.25 mg of 1,24-corticotropin (Synacthen; CIBA, Switzerland; corresponding to 25 IU ACTH) for measurement of basal and stimulated cortisol levels.

Cortisol production was defined as "adequate" when the baseline level was greater than 500 nmol/l (to convert values for cortisol to μg/dl, divide by 27.5) and the increase after ACTH was greater than 200 nmol/l, or the baseline level was already above 1000 nmol/l (see "Discussion"). Following the corticotropin test all patients were given a bolus injection of 100 mg hydrocortisone (Pharmacia & UpJohn, Germany), followed by a continuous infusion. This infusion was given at a rate of 10 mg/h for 7 days, was reduced to 6 mg/h on day 8, and then reduced by 2 mg/h per day until it was discontinued on day 10. Plasma samples for determination of plasma cortisol and transcortin levels were drawn daily between 6 and 8 a.m. Measurements were performed en bloc, and the results were therefore not available to the physicians treating the patients.

Analytical methods

Plasma cortisol was measured by solid-phase radioimmunoassay (Biermann, Bad Nauheim, Germany). Plasma transcortin was de-

Table 1 Patient characteristics and basal and stimulated cortisol levels

Patient no.	Fatal outcome on day	Age (years)	Sex	Focus	Causative organism	Plasma cortisol before ACTH	Plasma cortisol following ACTH (nmol/l)
1	16	56	M	Pneumonia	Pneumococci	901	950
2		39	F	Pneumonia	Not identified	203	269
3		65	M	Pneumonia	*Pseudomonas*	606	706
4	19	61	M	Pneumonia	Pneumococci	883	992
5		49	M	Pneumonia	Not identified	458	610
6		56	M	Pneumonia	*Staphylococcus aureus*	601	675
7		82	M	Urosepsis	*Escherichia coli*	854	907
8		55	M	Urosepsis	*Escherichia coli*	560	870
9	21	67	M	Pneumonia	*Legionella*	780	820
10	28	64	M	Pneumonia	Not identified	945	1105
11	16	75	F	Pneumonia	*Pseudomonas*	620	800
12		50	M	Pneumonia	Pneumococci	1875	2020
13	26	34	M	Endocarditis	*Staphylococcus aureus*	852	1056
14	6	70	M	Peritonitis	Not identified	965	1235
15	21	69	M	Peritonitis	Not identified	1068	1240
16		64	F	Meningitis	*Staphylococcus aureus*	1662	1732
17		64	F	Urosepsis	*Escherichia coli*	1345	1625
18		30	M	Pneumonia	Not identified	800	960
19		47	M	Pneumonia	Not identified	2169	2253
20	16	77	F	Peritonitis	*Escherichia coli*	545	800
Median						853	955
25–75 %						602–1042	800–1239

termined using a competition radioimmunoassay (Medgeniox Diagnostics, Fleurus, Belgium). The concentration of free cortisol was calculated from total cortisol and transcortin concentrations using the following formula: free cortisol (μmol/l) = $(Z^2+0.00128\ C–Z)^{-1/2}$, with Z = 0.0167+0.182 (T–C) [C = total cortisol (μmol/l); T = transcortin (μmol/l)] [25].

Statistics

For comparison of differences between groups the Mann-Whitney *U* test was used. Fisher's exact test was used to test for dependencies between groups. A p value less than 0.05 was considered significant. All statistics were computed using SPSS for Windows, version 7.0. Unless otherwise indicated values are presented as medians with the interquartile range in parenthesis.

Results

Basal and ACTH-stimulated cortisol levels

Basal and stimulated cortisol levels of the 20 patients studied are given in Table 1. Both basal and stimulated cortisol levels varied considerably, ranging from 203 to 2169 and from 269 to 2253 nmol/l, respectively.

Cortisol production was considered "adequate" in 9 patients because their cortisol level increased by at least 200 nmol/l following synacthen (nos. 8, 13, 14, 17, 20), which most investigators consider as a normal response [23], or the pre-ACTH concentration was already above 1000 nmol/l (nos. 12, 15, 16, 19; see "Discussion"). In the remaining 11 patients endogenous cortisol production was defined as "inadequate" because there was neither a response to ACTH of at least 200 nmol/l nor a baseline concentration of more than 1000 nmol/l. In one female patient (no. 2) cortisol levels were strikingly low. She had no evidence, however, of preexisting adrenal insufficiency, and after recovery her endogenous basal cortisol level increased to 545 nmol/l (day 14).

Comparison of patients with and without adequate cortisol production

The median basal levels of total cortisol were 780 nmol/l (601–883) in patients with "inadequate" and 1068 nmol/l (706–1769) in patients with "adequate" cortisol production ($p < 0.05$; Table 2). The concentrations of free cortisol, as derived from the determination of transcortin and total cortisol levels, were 263 nmol/l (154–381) and 104 (79–154) in both groups ($p < 0.01$) and thus amounted to about 24.6 % and 13.3 % of the total cortisol concentration. It should be noted that the formula does not include albumin, which also binds cortisol at a lower affinity. Although this may lead to a slight overestimation of the fraction of free cortisol, plasma albumin levels were low (2.85 g/dl, 2.62–3.53) and did not change significantly during the course of the study. Following ACTH administration the increment in median total cortisol level was 16.1 % and 5.1 %, respectively. Pa-

Table 2 Baseline characteristics of patients with and without "adequate" cortisol production *(CP)*; where appropriate, values are medians and interquartile range (*APACHE II* Acute Physiology and Chronic Health Evaluation II, *ARDS* acute respiratory distress syndrome, *ARF* acute renal failure, *BP* blood pressure)

	Inadequate CP ($n = 11$)	Adequate CP ($n = 9$)	p
Age (years)	61 (49–67)	64 (48.5–69.5)	0.97
Sex: M/F	9/2	6/3	0.40
APACHE II	29 (24–31)	25 (23.5–27.8)	0.34
Time from onset of septic shock (h)	36 (24–72)	48 (42–72)	0.11
Organ dysfunction			
ARDS	3 (27 %)	3 (33 %)	0.51
ARF	10 (83 %)	7 (78 %)	0.68
Causative organism			
Gram positive	3	3	0.96
Gram negative	4	3	0.96
Not identified	4	3	0.81
Systolic BP (mmHg)	118 (88–132)	106 (101–133)	0.79
Catecholamines (mg/d)			
Noradrenaline	36 (7.2–48)	48 (12–48)	0.88
Dopamine	360 (240–480)	240 (240–480)	0.55
Total cortisol (nmol (l)	780 (601–883)	1068 (706–1769)	< 0.04
Transcortin (mg/l)	23.3 (16.9–39.1)	27.4 (17.9–38.7)	0.90
Free cortisol (nmol/l)	104 (79–154)	263 (154–381)	< 0.01

tients in the two groups did not differ with respect to their demographic data, disease severity, as assessed by APACHE II score levels, organ dysfunction indices, the type of causative organisms, hemodynamics, or catecholamine doses.

Plasma cortisol levels following hydrocortisone therapy

The time course of total and free cortisol levels during the hydrocortisone treatment period in patients with and without "adequate" endogenous cortisol production is illustrated in Fig. 1. The median total cortisol level of all patients rose to 3587 nmol/l (2679–5220) on day 1 after the initiation of hydrocortisone therapy and subsequently declined to 1310 nmol/l (1156–1844) on day 7, despite the administration of a constant dose of 10 mg/h during this period. Total cortisol levels in patients with "inadequate" endogenous cortisol production were lower on day 1 [2843 (1900–3843) vs. 5025 (3192–5757); $p < 0.05$)], but were not significantly different on any other day.

Transcortin concentrations on days 2, 7, and 14 were 30.4 (20.7–44.4), 25.4 (16.3–29.8), and 23.2 mg/l (15.8–29.9) in patients with and 24.5 (17.5–36.4), 27.1 (23.4–36.1), and 29.8 mg/l (19.7–35.1) in patients without "adequate" endogenous cortisol production and thus did not differ between the groups.

Free cortisol levels that were calculated from total cortisol and transcortin concentrations rose 8.5-fold to a median of 1210 nmol/l (750–1846) following the initiation of hydrocortisone therapy and did not differ between patients with and those without "adequate" endogenous cortisol production (Fig. 1, lower panel).

Before the initiation of hydrocortisone therapy patients on renal replacement therapy had lower total and free cortisol levels [620 (545–803) and 95 (79–196) vs. 945 (853–1503) and 262 (129–337) nmol/l; $p < 0.04$). However, during hydrocortisone therapy cortisol levels did not differ between patients receiving and those not receiving hemodialysis or hemofiltration, with the exception of day 2, when free cortisol was even higher in patients on renal replacement therapy [1057 (802–1481) vs. 430 (290–924) nmol/l; $p < 0.01$]. Thus, as expected from the molecular size of cortisol, blood purification did not seem to contribute to differences or to the reduction in cortisol levels with prolonged therapy.

Hemodynamics and outcome following hydrocortisone therapy

In all but two patients catecholamines could be reduced during the observation period. Although systolic and mean arterial blood pressure blood did not differ between patients with and without "inadequate" cortisol production (Table 3), the rate of reduction in noradrenaline did differ. Figure 2 illustrates that patients with "inadequate" cortisol production required 15 % (5–25 %) of the initial noradrenaline dose on day 2. In contrast, in patients with "adequate" cortisol production noradrenaline could only be reduced by 50 % (21–88 %; $p < 0.01$). In addition, patients with "inadequate" cortisol production were free of vasopressor sup-

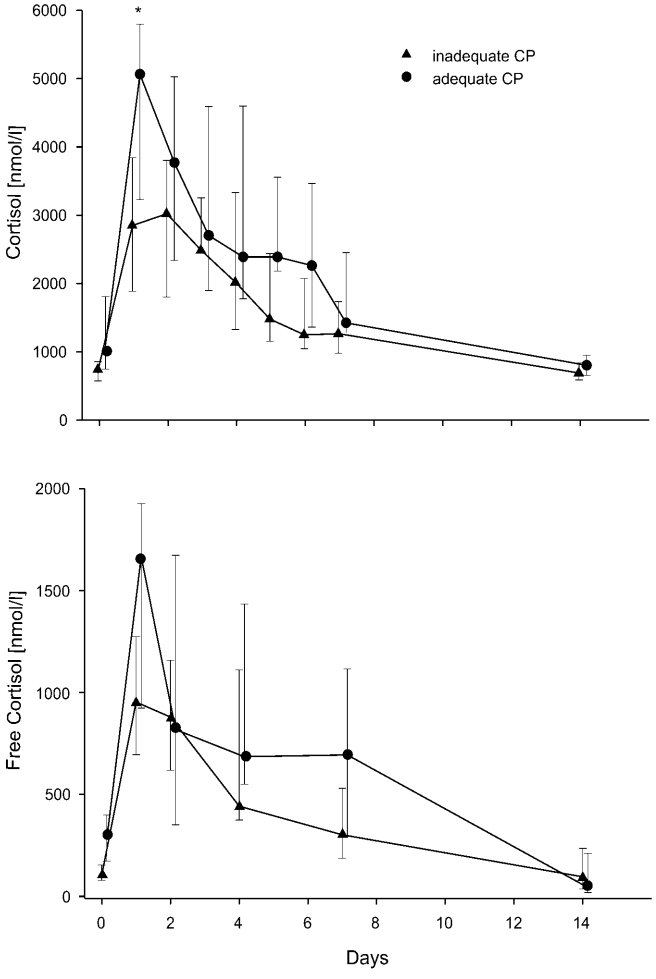

Fig. 1 Kinetics of plasma total cortisol (a) and free cortisol (b) in patients with septic shock receiving "low-dose" hydrocortisone therapy. Values are median and interquartile range. *$p < 0.005$ between total cortisol level in patients with adequate and patients with inadequate endogenous cortisol production *(CP)*

port significantly earlier than patients with "adequate" cortisol production (Table 3). There was, however, no difference in survival or the course of inflammatory parameters between the two groups (Table 3).

Comparison of patients with and without a rapid hemodynamic improvement following hydrocortisone therapy

To identify patient characteristics other than endogenous cortisol production that determine hemodynamic improvement during hydrocortisone therapy patients were divided into two groups according to whether the catecholamine dose could be reduced by at least 70% within 48 h. Fourteen of the 20 patients investigated fulfilled this criterion. As shown in Table 4, the only detectable difference between patients with and without rapid weaning from catecholamines was their endogenous cortisol production; 11 of 14 patients with rapid hemodynamic improvement, but none of the 6 patients with continued high catecholamine dependence, showed inadequate endogenous cortisol production. Accordingly, free and total cortisol levels before the initiation of hydrocortisone therapy in patients with early improvement were significantly lower. During the course of corticosteroid therapy, however, cortisol levels were very similar in the two groups. There was also no difference between the groups with respect to patient demographics, the disease severity score, or the course of inflammatory parameters.

Table 3 Clinical course of patients with and without "adequate" cortisol production (CP); values are medians and interquartile range (*CRP* C-reactive protein, *PCT* procalcitonin)

	Inadequate CP ($n = 11$)	Adequate CP ($n = 9$)	p
MAP (mmHg)			
Day 0	68 (59–82)	71 (81–88)	0.31
Day 2	91 (82–99)	88 (84–94)	0.61
Day 7	92 (85–100)	90 (84–96)	0.71
CRP (mg/dl)			
Day 0	18.4 (10.7–33.3)	20.3 (12.8–30.3)	0.71
Day 2	16.4 (10.8–35.5)	12.8 (9.9–30.7)	0.66
Day 7	1.9 (1.1–9.9)	1.6 (0.9–2.7)	0.35
PCT (ng/ml)			
Day 0	19.5 (3.4–172)	13.4 (1.6–120)	0.50
Day 2	12.9 (3.2–204)	5.3 (1.7–83)	0.45
Day 7	3.8 (0.8–28)	2.6 (1.8–15.6)	0.72
WBC/nl			
Day 0	18.4 (3.8–20.0)	11.0 (4.8–22.5)	0.87
Day 2	13.5 (9.0–18.0)	11.9 (10.0–16.7)	0.87
Day 7	9.9 (8.9–18.4)	13.5 (10.8–31.1)	0.45
Body temp. (°C)			
Day 0	39.1 (38.0–40.1)	38.7 (37.6–39.6)	0.67
Day 2	37.0 (36.5–37.6)	37.0 (36.8–37.6)	0.96
Day 7	37.5 (36.9–37.7)	37.2 (36.8–37.8)	0.78
Free of vasopressors after days	3 (2–3)	5 (3.5–10.5)	< 0.01
Deaths	5 (45%)	4 (44%)	0.96

Comparison of pretreatment cortisol status between survivors and nonsurvivors

The pretreatment cortisol status did not differ between survivors ($n = 11$) and nonsurvivors ($n = 9$). Respective levels for total cortisol were 800 (560–1662) and 883 nmol/l (700–955). Free cortisol levels also did not differ between the two groups [103 (79–376) vs. 187 (115–242) nmol/l]. The endogenous cortisol production

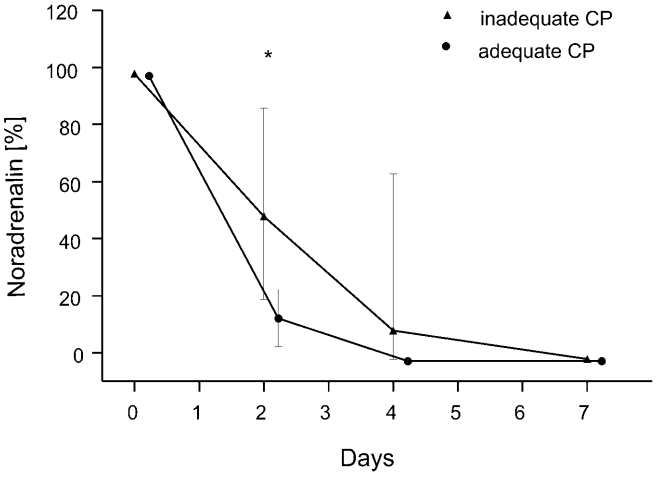

Fig. 2 Time course of noradrenaline needs in patients with and without adequate endogenous cortisol production *(CP)*. Two days after the beginning of "low-dose" hydrocortisone therapy patients with inadequate endogenous production needed significantly less vasopressor support

was considered "inadequate" in 6 of 11 survivors and in 5 of 9 nonsurvivors.

Discussion

This study confirms that endogenous plasma cortisol concentrations are increased in patients with septic shock, but that the degree of increase is highly variable. Only one of 20 patients had a post-ACTH cortisol plasma level less than 500 nmol/l, which supports the concept that absolute adrenocortical deficiency is rare in critically ill patients [5, 6, 7, 26, 27, 28, 29, 30, 31]. Whether increases in cortisol levels are appropriate for the severity of illness or reflect functional hypoadrenalism is less clear. The rapid ACTH test is widely used as a simple method to identify adrenocortical hyporesponsiveness, but controversy exists as to how diagnostic criteria should be derived from the basal cortisol level, the stimulated cortisol level or their difference [24]. Three [6, 7, 32] of four previous studies [6, 7, 28, 32] using a rapid ACTH test to investigate adrenocortical function in septic shock used an increment of at least 200–250 nmol/l to define "adequate" responsiveness. However, in healthy controls, large unselected patient populations and also in patients with septic shock [7, 24] (Table 1) cortisol increments are inversely related to basal levels. As discussed previously [24, 29, 31, 33, 34], it appears likely that disproportionately low increments from high basal cortisol concentrations are due to maximal endogenous ACTH and therefore not indicative of adrenocorticoid hyporesponsiveness. We have thus arbitrarily defined endogenous cortisol production as "adequate" in patients not only when they responded significantly to ACTH, but also when their baseline level was above 1000 nmol/l. Using these criteria endogenous cortisol production appeared to be "inadequate" in approximately one-half of our patients. It should be noted, however, that an elevation in plasma cortisol levels above 1000 nmol/l in septic patients may reflect not only increased production but could also indicate decreased hepatic cortisol clearance [35, 36].

Following cortisol therapy with a similar dose as in previous trials (340 mg/day) [18, 19, 20, 21], peak concentrations of total cortisol were almost threefold higher than the post-ACTH level in patients considered to have an "adequate" endogenous response. These peak concentrations corresponded to a 6.2-fold and 9.1-fold increase in free cortisol concentrations in patients with and without "adequate" endogenous production. Clearly therefore this dose must be considered as supraphysiological. Interestingly, although the median total cortisol level remained above 1000 nmol/l thereafter, the levels of both total and free cortisol declined progressively during the course of therapy despite the administration of a constant dose of 10 mg/h. A similar, albeit less pronounced reduction in cortisol levels during "low-dose" hydrocortisone therapy has also been reported by Briegel et al. [22]. However, in this study the dose was tapered after only 1–5 days. Therefore, in contrast to our observations, the decline could be attributed to the reduction in steroid dose. Even if one assumes that in the present investigation the administration of ACTH and the initial bolus injection of 100 mg contributed to the peak concentration on day 1, and that endogenous cortisol production was subsequently suppressed, these two effects cannot entirely explain the reduction in median level from 3587 to 1310 nmol/l between days 1 and 7. Moreover, it has been shown that cortisol production in septic shock is in fact not suppressible by steroids [34]. It is possible therefore that the metabolism of hydrocortisone changes during the treatment period. Earlier studies have shown that cortisol extraction from blood is decreased, and that its half-life is prolonged during septic shock [35, 36]. The observed decline in cortisol levels during the treatment period could reflect a reversal of these alterations.

Our intention in this study was not to compare the efficacy of cortisol therapy to untreated controls. It is nevertheless noteworthy that inotropes could be reduced rather quickly after initiation of the hydrocortisone infusion. The reduction in catecholamine dose was comparable [21] or even faster than in previous studies using similar doses of cortisol [18, 20], which may be related to the fact that we started therapy earlier during the septic course. In contrast to previous reports [6, 7, 28], mortality in patients with "inadequate" endogenous cortisol was not higher (Table 2), and survivors and nonsurvivors did not have significantly different steroid levels

Table 4 Characteristics of patients with and without rapid hemodynamic improvement following the initiation of hydrocortisone therapy, defined as a reduction in noradrenaline requirement of at least 70 % within 48 h following the initiation of hydrocortisone therapy; values are medians and interquartile range (*APACHE II* Acute Physiology and Chronic Health Evaluation II, *ARDS* acute respiratory distress syndrome, *ARF* acute renal failure, *CRP* C-reactive protein, *PCT* procalcitonin)

	Rapid hemodynamic improvement ($n = 14$)	No rapid hemodynamic improvement ($n = 6$)	p
Age (years)	62.5 (53.5–69)	57 (43.8–69.3)	0.66
Sex: M/F	10/4	5/1	
APACHE II	28, 5 (24–31)	25 (21–26, 5)	0.13
Organ dysfunction			
ARDS	4 (29 %)	2 (33 %)	0.52
ARF	13 (93 %)	5 (83 %)	0.13
Deaths	6 (42 %)	3 (50 %)	0.54
Cortisol production			
Inadequate	11 (79 %)	0	< 0.01
Adequate	3 (21 %)	6 (100 %)	< 0.01
Total cortisol (nmol/l)			
Day 0	700 (556–887)	1365 (937–1949)	< 0.002
Day 1	3345 (2335–4805)	4280 (2825–6600)	0.40
Day 2	3137 (2418–3947)	3480 (1904–4903)	0.72
Day 7	1305 (1013–1844)	1383 (1252–1886)	0.54
Free cortisol (nmol/l)			
Day 0	96.6 (83.1–165.1)	328 (220–397)	< 0.001
Day 1	1210 (733–1527)	1391 (799–2116)	0.70
Day 2	955 (681–1251)	586 (291–1431)	0.42
Day 7	345 (221–586)	493 (188–989)	0.52
CRP (mg/dl)			
Day 0	19.1 (12.2–30.1)	27.0 (11.1–47.0)	0.56
Day 2	16.1 (10.2–31.2)	14.7 (9.3–35.5)	0.89
Day 7	1.7 (1.1–8.4)	2.4 (0.7–3.8)	0.77
PCT (ng/ml)			
Day 0	21.1 (3.1–212)	8.5 (1.9–68)	0.32
Day 2	8.3 (3.6–172)	10.1 (0.8–54)	0.37
Day 7	5.4 (1.4–15.6)	2.5 (1.1–7.8)	0.70
WBC/nl			
Day 0	14.3 (3.4–21.2)	11.8 (4.9–27.1)	0.95
Day 2	14.6 (9.3–17.3)	10.4 (9.6–18.9)	0.74
Day 7	11.3 (9.3–20.3)	15.7 (9.4–16.1)	0.94
Body temp. (°C)			
Day 0	39.0 (37.9–39.6)	39.4 (37.7–40.1)	0.88
Day 2	37.0 (36.9–37.6)	37.0 (36.5–37.9)	0.80
Day 7	37.2 (37.0–37.6)	37.5 (36.2–38.5)	0.84

before hydrocortisone therapy. This observation is in accordance with the results of a recent randomized controlled trial by Bollaert et al. [20] and is compatible with the growing evidence that "low-dose" therapy reverses the putative adverse risk factor of inappropriate cortisol production [18, 19, 20, 21, 22].

Although patients with "adequate" and "inadequate" endogenous production were clinically indistinguishable at the onset of therapy (Table 2), and did not have significantly different levels of free cortisol during hydrocortisone therapy (Fig. 1), those with "inadequate" endogenous response showed a significantly faster reduction in their vasopressor support (Fig. 2). In addition, the only detectable difference between patients with and without rapid hemodynamic improvement was their basal cortisol status (Table 4). Similarly Briegel et al. [18] found that 6 of 14 patients weaned from catecholamines within 48 h of hydrocortisone therapy had lower cortisol levels before steroid treatment. In addition, Annane et al. [32] reported that patients in septic shock with inadequate as compared to adequate cortisol production had lower baseline responsiveness to noradrenaline but showed a more marked improvement in vasopressor sensitivity in response to hydrocortisone bolus. It appears therefore that the greatest benefit of hydrocortisone therapy is achieved in patients with blunted endogenous production, although the exact mechanisms of this sensitization remain to be elucidated. In contrast to the hemodynamic changes the febrile response and the course of C-reactive protein and procalcitonin levels or white blood cell counts did not depend on the pretreatment cortisol production (Table 3).

Thus, although it has been suggested that hydrocortisone treatment reduces indicators of the acute-phase response [22], these effects appear not to be directly related to the hemodynamic effects. We also found no association between the hemodynamic response and survival rates (Table 4), but larger controlled trials are necessary to exclude or verify effects on such outcome parameters.

In conclusion, there are three main findings of this study. Firstly, during proposed regimes of "low-dose" hydrocortisone therapy plasma cortisol concentrations are achieved initially which considerably exceed basal and ACTH stimulated levels. Thus in order to achieve a substitution of deficient endogenous production, doses even lower than those used so far may be sufficient. Secondly, during continuous administration of hydrocortisone, cortisol levels decline, suggesting that changes in cortisol metabolism have a significant impact on its plasma concentration. Thirdly, "inadequate" endogenous steroid production appears to sensitize patients to the hemodynamic effects of a rise in plasma cortisol levels.

References

1. American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20: 864–874
2. Hardaway RM (2000) A review of septic shock. Am Surg 66: 22–29
3. Dorin RJ, Kearne PJ (1988) High output circulatory failure in acute adrenal insufficiency. Crit Care Med 16: 296–297
4. Hinshaw LB, Beller FK, Change ACK, et al (1985) Corticosteroid treatment of adrenalectomised dogs challenged with lethal E. coli. Circ Shock 16: 265
5. Sibbald WJ, Short A, Cohen MP, Wilson RF (1977) Variations in adrenocortical responsiveness during severe bacterial infections. Ann Surg 186: 29–33
6. Rothwell PM, Udwadia ZF, Lawler PG (1991) Cortisol response to corticotropin and survival in septic shock. Lancet 337: 582–583
7. Moran JA, Chapman MJ, O'Fathartaigh MS, Peisach AR, Pannall PR, Leppard P (1994) Hypocortisolemia and adrenocortical responsiveness at onset of septic shock. Intensive Care Med 20: 489–495
8. Lamberts SWJ, Bruining HA, De Jong FH (1997) Corticosteroid therapy in severe illness. N Engl J Med 337: 1285–1292
9. Santos AA, Scheltinga MR, Lynch E, et al (1993) Elaboration of interleukin 1-receptor antagonist is not attenuated by glucocorticoids after endotoxemia. Arch Surg 128: 138–144
10. Jarek MJ, Legare EJ, McDermott MT, Merenich JA, Kollef MH (1993) Endocrine profiles for outcome prediction from the intensive care unit. Crit Care Med 21: 543–550
11. Rothwell PM, Lawler PG (1995) Prediction of outcome in intensive care patients using endocrine parameters. Crit Care Med 23: 78–83
12. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellisant E (2000) A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 283: 1038–1045
13. Sprung CL, Caralis PV, Marcial EH, et al (1984) The effects of high-dose corticosteroids in patients with septic shock. N Engl J Med 311: 1137–1143
14. Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA (1987) A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 317: 653–658
15. The veterans administration systemic sepsis cooperative study group (1987) Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. N Engl J Med 317: 659–665
16. Cronin L, Cook DJ, Carlet J, et al (1995) Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. Crit Care Med 23: 1430–1439
17. Lefering R, Neugebauer EAM (1995) Steroid controversy in sepsis and septic shock: a metaanalysis. Crit Care Med 23: 1294–1303
18. Briegel J, Forst H, Helinger H, Haller M (1991) Contribution of cortisol deficiency to septic shock. Lancet 338: 507–508
19. Schneider J, Voerman HJ (1991) Abrupt hemodynamic improvement in late septic shock with physiological doses of glucocorticoids. Intensive Care Med 17: 436–437
20. Bollaert P, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A (1998) Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 26: 645–650
21. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, Hemmer B, Hummel T, Lenhart A, Heyduck M, Stoll C, Peter K (1999) Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double blind, single center study. Crit Care Med 27: 723–732
22. Briegel J, Kellerman W, Forst H, et al (1994) Low-dose hydrocortisone infusion attenuates the systemic inflammatory response syndrome. Clin Investig 72: 782–787
23. Speckart PF, Nicoloff JT, Bethune JE (1971) Screening for adrenocortical insufficiency with cosyntropin. Arch Intern Med 128: 761–763
24. May ME, Carey RM (1985) Rapid adrenocorticotropic hormone test in practice. Am J Med 79: 679–684
25. Coolens JL, van Baelen H, Heyns W (1987) Clinical use of unbound plasma cortisol as calculated from total cortisol and corticosteroid binding globulin. J Steroid Biochem 197–202
26. Span LFR, Hermus ARMM, Bartelink AKM, et al (1992) Adrenocortical function: an indicator of severity of disease and survival in chronic critically ill patients. Intensive Care Med 18: 93–96
27. Jurney TH, Cockrell JL, Lindberg JS, Lamiell JM, Wade CE (1987) Spectrum of serum cortisol response to ACTH in ICU patients. Chest 92: 292–293
28. Soni A, Pepper GM, Wyrwinski PM, et al (1995) Adrenal insufficiency occurring during septic shock: incidence, outcome, and relationship to peripheral cytokine levels. Am J Med 98: 266–271
29. Schein RMH, Sprung CL, Marcial E, Napolitano L, Chernow B (1990) Plasma cortisol levels in patients with septic shock. Crit Care Med 18: 259–263
30. Briegel J, Schelling G, Haller M, Mraz W, Forst H, Peter K (1996) A comparison of the adrenocortical response during septic shock and after complete recovery. Intensive Care Med 22: 894–899

31. Bouachour G, Tirot P, Gouello JP, Mathieu F, Vincent JF, Alquier P (1995) Adrenocortical function during septic shock. Intensive Care Med 21: 57–62
32. Annane D, Bellisant E, Sebille V, Lesieur O, Mathieu B, Raphael JC, Gajdos P (1998) impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve. Br J Clin Pharmacol 46: 589–597
33. Oelkers W (1996) Adrenal insufficiency. N Engl J Med 335: 1206–1212
34. Perrot D, Bonneton A, Dechaud H, Motin J, Pugeat M (1993) Hypercortisolism in septic shock is not suppressible by dexamethasone infusion. Crit Care Med 21: 396–401
35. Melby JC, Spink WW (1958) Comparative studies on adrenal cortical function and cortisol metabolism in healthy adults and in patients with shock due to infection. J Clin Invest 37: 1791–1798
36. Melby JC, Egdhal RH, Spink WW (1960) Secretion and metabolism of cortisol after injection of endotoxin. J Lab Clin Med 56: 50–62