A comparison of the adrenocortical response during septic shock and after complete recovery

Abstract

Objective: To compare the adrenocortical response to corticotropin during septic shock and after complete recovery.

Design: Prospective clinical study.

Setting: Multidisciplinary intensive care unit in a university hospital.

Patients: 20 consecutive patients surviving septic shock. All patients met the American College of Chest Physicians/Society of Critical Care Medicine criteria for septic shock. In addition, the presence of high-output circulatory failure with a cardiac index > 4.1/min per m² was a criterion for enrollment in the study. Complete recovery from septic shock was defined as discontinuation of any supportive therapies. Severity of illness during septic shock and after recovery was graded using the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system.

Interventions: In each patient, two short corticotropin stimulation tests were done during septic shock and after recovery.

Measurements and results: Basal cortisol levels recorded during septic shock and after recovery did not differ (medians: 18.8 vs 18.9 μg/dl). However, the response to corticotropin was significantly attenuated during septic shock when compared with the response after recovery (medians: 7.7 vs 14.7 μg/dl; p = 0.02). After recovery, patients' stress response was less, as indicated by a reduction in APACHE II scores (medians: 21 vs 5 points; p < 0.01)

Conclusions: Adrenocortical response to corticotropin is attenuated in patients with septic shock and high-output circulatory failure compared to the response in the much less stressful condition after recovery. The attenuated adrenocortical responsiveness may be explained by effects of circulating mediators from the systemic inflammatory response.

Key words Septic shock · Cortisol · ACTH · Adrenocortical insufficiency · Hemodynamics

Introduction

In patients with septic shock, serum cortisol concentrations are usually elevated compared with those in un-stressed, healthy individuals [1, 2]. Hypercortisolemia mainly results from increased secretion of cortisol due to activation of the pituitary-adrenal axis and from decreased clearance of cortisol [3]. It is assumed that cortisol concentrations of more than 20 μg/dl are appropriate for tissue requirements in septic shock [1, 2].

However, during septic shock, the secretory reserve of cortisol may be reduced. Sepsis has been shown to decrease corticotropin-induced steroidogenesis [3, 4], and several studies report a subset of septic shock patients with a subnormal response to 0.25 mg corticotropin [5–8]. It has been suggested that the subnormal response...
to corticotropin in the presence of supranormal cortisol levels is due to relative adrenocortical insufficiency [5–8].

A recent study investigated the incidence of relative adrenocortical insufficiency in patients with septic shock [2]. The authors applied different criteria for relative adrenocortical insufficiency as reported in earlier studies and found the incidence to vary from 6.25 to 75%, depending on the criteria used [2]. Whether an impairment of the adrenal reserve really affects patients with septic shock remains unclear due to these methodological problems. Another way to demonstrate relative adrenocortical insufficiency, which was used in this study, is to compare the adrenocortical response to corticotropin during septic shock and after recovery, using each patient as his or her own control.

Patients and methods

The study protocol was approved by the Institutional Review Board of the University of Munich. Voluntary informed consent was obtained from the next of kin.

Patients

Patients suffering from septic shock were enrolled in the study if they met the criteria of septic shock proposed by the members of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee, i.e. documented infection or positive blood culture; at least two symptoms of a systemic inflammatory response syndrome such as fever (body temperature >38°C) or hypothermia (<36°C), tachycardia (>90 beats/min), tachypnea (>20 breaths/min), and abnormal white blood cell counts (>12000/μl or <4000/μl); use of vasopressor support (dopamine >6 μg/kg per min or norepinephrine added to dopamine) despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction [9]. Furthermore, we studied only patients with high-output circulatory failure, defined as a cardiac index of more than 4.01/min per m² (in patients >55 years: >3.51/min per m²). Patients were excluded if they had received glucocorticoids or etomidate 24 h prior to the corticotropin stimulation test or if they died during the course of their disease. All patients were monitored invasively by means of a Swan-Ganz-catheter and an arterial line. Patients received conventional therapy for septic shock, including antibiotics, fluid resuscitation, vasopressor and positive inotrope therapy, mechanical ventilation, and, in cases of acute renal failure, hemofiltration. Patients in septic shock were deeply sedated with a continuous infusion of midazolam and fentanyl. When the severe acute respiratory distress syndrome (ARDS), as defined by the American-European Consensus Conference [10], was diagnosed, pancuronium was used for neuromuscular relaxation. If the patients met the criteria of the American extracorporeal membrane oxygenation study [11], extracorporeal lung assist was instituted using a heparin-coated by-pass system.

In addition, 17 patients (12 survivors and 5 non-survivors) received stress doses of hydrocortisone (0.18 mg/kg per h) after the short corticotropin stimulation test was completed. This dose corresponds to a maximum secretory rate of cortisol found in patients following major surgery [12]. When septic shock had been reversed, the dose of hydrocortisone was reduced to 0.08 mg/kg per h. As soon as the underlying infection had been treated successfully, hydrocortisone was tapered step-by-step over a few days. The second corticotropin stimulation test was performed at least 24 h after hydrocortisone had been withdrawn.

Methods

After fluid resuscitation, titration of vasopressors, and institution of life-supportive therapy, a short corticotropin stimulation test was performed. Arterial blood samples were drawn prior to (basal cortisol level) and 60 min (peak cortisol level) after injection of 0.25 mg tetracosactide (Synacthen, Ciba-Geigy, Wehr, Germany). In septic shock, the maximum response to corticotropin has been noted 60 min after injection [5, 6]. Therefore, we chose this time point to assess the maximum response to corticotropin.

If discharge from the ICU was considered, a second short corticotropin stimulation test was done as described above. At the time of this measurement, antibiotics and life-support therapies (vasopressor therapy, mechanical ventilation, hemofiltration, or extracorporeal lung assist) had been discontinued. The severity of illness during septic shock and after recovery was graded using the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system [13].

Statistical analysis

Since the data were not normally distributed, medians and ranges are given and nonparametric tests were used for analysis. Comparisons were made using the Mann-Whitney U test for independent groups and the Wilcoxon matched-pairs signed-ranks test for paired data, respectively. Correlations were calculated using correlation analysis (Pearson’s r); p values < 0.05 were considered statistically significant. Statistics were calculated using the SPSS+(version 6.1) computer package (SPSS, Chicago, Ill., USA).

Results

During a 24-month period, 33 patients fulfilled the entry criteria and 13 patients succumbed to septic shock or multiorgan failure. The basal cortisol levels and the response to corticotropin did not differ between survivors and nonsurvivors: [basal cortisol: median 18.8 μg/dl (range 7.1–52.5 μg/dl) vs 23.3 μg/dl (range 5.0–55.8 μg/dl), p = 0.42; cortisol response: median 7.65 μg/dl (range –0.9–32.9 μg/dl) vs 4.4 μg/dl (ranges –1.4–23 μg/dl), p = 0.70].

Clinical characteristics of the patients, such as biometric data, diagnoses, presumptive sources of infection, microorganisms isolated, and data on organ dysfunction at the time of the short corticotropin stimulation test during septic shock, are given in Table 1. The APACHE II score, the basal cortisol level, and the cortisol response to 0.25 mg tetracosactrin given intravenously during septic shock and after recovery are shown in Table 2. The median interval between the two short corticotropin stimulation tests was 30.5 days (range 11–123).

Basal cortisol levels in septic shock varied widely (range 7.1–52.5 μg/dl) compared with cortisol levels after...