Intensive Care Med (2006) 32:595–598
DOI 10.1007/s00134-005-0046-9

BRIEF REPORT

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Cortisol levels in patients with severe community-acquired pneumonia

Received: 22 September 2005
Accepted: 16 December 2005
Published online: 28 January 2006

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Abstract *Objectives:* To evaluate cortisol levels and prevalence of adrenal insufficiency in patients with severe community-acquired pneumonia (CAP). *Design and setting:* Retrospective cohort study in a 24-bed medical-surgical intensive care unit (ICU). *Patients:* Forty patients with severe CAP admitted to the ICU from March 2003 and May 2005. *Measurements and results:* Random cortisol levels were measured up to 72 h after ICU admission. A threshold of 20 μg/dl was considered for the diagnosis of adrenal insufficiency. Median cortisol levels were 15.5 μg/dl (IQR 10.8–25.1), and 26 patients (65%) met the criteria for adrenal insufficiency. Other cutoff levels of cortisol were evaluated, and 30 patients (75%) had cortisol levels below 25 μg/dl and 19 (47.5%) had cortisol levels below 15 μg/dl. When only patients with septic shock ($n = 19$) were evaluated, 12 (63%) had adrenal insufficiency. *Conclusions:* Relative adrenal insufficiency occurs in a high proportion of patients with severe CAP. This finding highlights the importance of measuring cortisol levels and may help explain the potential benefits of hydrocortisone infusion in these patients.

Keywords Community-acquired pneumonia · Adrenal insufficiency · Hydrocortisone · Acute respiratory failure · Sepsis · Cortisol

Introduction

Interactions between the endocrine and immune systems are well recognized. Complex changes in the endocrine system have recently been described in critical illness [1]. Severe infections and the immune response to microorganisms are frequently implicated in the endocrine alterations present in critically ill patients, particularly those of the hypothalamic-pituitary-adrenal axis. Therefore relative or functional adrenocortical insufficiency occurs despite elevated cortisol levels. Critically ill patients present with a blunted adrenal response to severe stress, and plasma cortisol levels often regarded as normal or elevated in normal subjects are therefore inappropriately low in critically ill patients [2]. Few years ago a randomized controlled trial demonstrated that treatment with supraphysiological doses of hydrocortisone improved survival of patients with septic shock and adrenal failure [3]. In addition, a recent study reported the effects of hydrocortisone infusion in patients admitted with severe community-acquired pneumonia (CAP) [4]. In this trial the authors observed significantly better rates of morbidity and mortality in patients receiving steroids than in controls. The physiological rationale for the potential benefits of steroid replacement in severe infections is based on the treatment of adrenal insufficiency and its immunomodulatory effects [2, 4]. This issue is not new, as the use of steroids as an adjunct therapy for pneumonia has been proposed for more than 60 years [5]; however, its benefits were never so apparent. However, the adrenal function of patients enrolled in this trial was not examined [4]. The aim of the present study was to evaluate cortisol levels and the prevalence of adrenal insufficiency in patients with severe CAP.

Patients and methods

Design and setting

This was a retrospective cohort study performed at a tertiary care hospital with a 24-bed medical-surgical intensive care unit (ICU) and was approved by the Institutional Review Board that waived the need of informed consent.

Selection of participants, data collection and definitions

We reviewed the charts and medical records of adult patients (age > 18 years) with severe CAP admitted to the ICU during the period of March 2003 and May 2005. Patients who had received steroids prior to cortisol measurement and those with a previous history of use of systemic steroids within the previous year were excluded ($n = 6$). Patients admitted because of terminal illnesses were also excluded ($n = 5$). There were 40 patients who fulfilled entry criteria and were evaluated. The main characteristics of the entire population and of subgroups stratified by adrenal function are presented in Table 1. Thirty patients (75%) had previous comorbidities, the most prevalent of which were chronic obstructive pulmonary disease ($n = 8$), type 2 diabetes ($n = 5$), cerebrovascular disease ($n = 4$), and cancer ($n = 3$).

The Acute Physiology and Chronic Health Evaluation II [6] and Sequential Organ Failure Assessment scores [7] were routinely calculated at ICU admission. Severe CAP was diagnosed according to the criteria of the British Thoracic Society [8]. Of the 40 patients 14 (35%) presented with two criteria, 20 (50%) with three, and 6 (15%) with all four criteria. For the purpose of this study the following criteria were used for the diagnosis of adrenal insufficiency: a random (stress) cortisol level < 20 μ/dl in patients with hypoxemic acute respiratory failure and hemodynamic instability [hypotension (systolic BP < 90 mmHg) or need of vasopressors]. Of the 40 patients 14 (35%) presented with two criteria, 20 (50%) with three, and 6 (15%) with all four criteria. Blood samples were drawn in the morning and cortisol levels were determined with a commercially available immunoassay kit (Roche Diagnostics, Indianapolis, Ind., USA). As part of the routine diagnostic work-up cortisol levels were obtained within the first 72 h of ICU admission and while patients presented with both hypoxic acute respiratory failure and hemodynamic instability. Cortisol results were available within 12–24 h after testing. The decision to treat patients with hydrocortisone (initial dose 300 mg/24 h) as well as the steroid weaning was at discretion of assistant intensivist. Etomidate, ketoconazole, and rifampicin were not used in any of the patients.

Data presentation and statistical analysis

All continuous variables were presented as median and 25th–75th percentiles (interquartile range, IQR) and were compared by Mann-Whitney test. Categorical variables were presented as numbers (percentage) and analyzed by the χ^2 or Fisher's exact test as appropriate. All statistical tests were two-tailed, and differences at a p value less than 0.05 were considered statistically significant.

Results

All patients received antimicrobial therapy according to the existing recommendations [9]; a combination of β-lactams and macrolides was used in 32 patients (80%) and fluoroquinolones in 8 (20%). Six patients (15%) had

Table 1 Patients' characteristics: medians (*parentheses* interquartile ranges) or numbers (*parentheses* percentage) (*APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment, *ICU* intensive care unit)

Variables	All patients ($n = 40$)	Cortisol levels < 20 μg/dl ($n = 26$)	Cortisol levels >20 μg/dl ($n = 14$)	p
Gender: M/F	19/21	14/12	5/9	0.44
Age (years)	74 (56–83)	70 (54–83)	80 (62–85)	0.24
APACHE II	16 (12–19)	16 (11–19)	17 (12–23)	0.36
SOFA (1st day of ICU)	4 (2–7)	4 (1–8)	5 (2–7)	0.39
Mechanical ventilation	28 (70%)	16 (61%)	12 (86%)	0.21
Duration of mechanical ventilation (days)	13 (9–23)	13 (9–20)	12 (5–27)	0.90
PaO_2/FIO_2 ratio at admission	280 (189–319)	280 (189–321)	290 (170–328)	0.86
Septic shock	19 (47.5%)	11 (42%)	6 (43%)	0.97
C-reactive protein (1st day of ICU) (mg/dl)	14.8 (11.4–21.3)	15.7 (11.6–26.4)	13.5 (9.1–16.2)	0.27
Albumin (g/dl)	2.3 (2–2.9)	2.3 (2.1–3.0)	2.3 (1.8–2.7)	0.49
Cortisol (μ/dl)	15.5 (10.8–25.1)	12.3 (10.1–15.5)	28.3 (23–36.5)	<0.001
Patients treated with hydrocortisone	23 (57.5%)	14 (54%)	9 (64%)	0.76
ICU stay (days)	13 (5–26)	12 (4–17)	22 (6–30)	0.09
ICU mortality	9 (22.5%)	6 (23%)	3 (21%)	0.9
Hospital mortality	13 (32.5%)	6 (23%)	7 (50%)	0.17

positive blood cultures (all of them for *Streptococcus pneumoniae*). Eighteen (45%) patients underwent bronchoalveolar lavage (ten with use of antibiotics for more than 24 h) and there were seven positive cultures [*S. pneumoniae* ($n = 3$), *Haemophilus influenza* ($n = 2$), *Klebsiella pneumoniae* ($n = 1$) and *Pseudomonas aeruginosa* ($n = 1$)].

Twenty-six patients (65%) met our criteria for adrenal insufficiency. Other cutoff levels of cortisol were also evaluated, and 30 patients (75%) had cortisol levels below 25 μg/dl and 19 (47.5%) below 15 μg/dl. When patients with septic shock ($n = 19$) were studied, 12 (63%) had cortisol levels below 20 μg/dl, a frequency that was similar to the total population regardless of the hemodynamic status ($p = 0.99$). Among patients with positive blood cultures five had cortisol levels less than 20 μg/dl, whereas 21 of 34 patients with negative blood cultures had cortisol levels less than 20 μg/dl (83% vs. 61.7%, $p = 0.39$). Differences between cortisol levels of patients with positive (median 11.9 μg/dl, IQR 10.4–20.9) and negative (16.9 μg/dl, 12.0–27.8) blood cultures were not statistically significant ($p = 0.26$). Cortisol levels (median 17.8 μg/dl, IQR 12.4–26.8, vs. 15.8 μg/dl, 10.1–34.4; $p = 0.73$) and the frequency of patients with adrenal insufficiency (61.5% vs. 48%; $p = 0.51$) did not differ between patients with or without hypoalbuminemia (albumin <2.5 g/dl).

Discussion

The present study observed random cortisol levels of patients admitted to the ICU with severe CAP. Patients presented with substantial severity of their illness that could predispose them to the development of adrenal insufficiency. Although adrenal response to the corticotropin test and free cortisol measurement were not assessed, random cortisol levels and a cutoff level of 20 μg/dl were used for the diagnosis of adrenal insufficiency [10, 11, 12]. A high frequency of adrenal insufficiency was found regardless of the chosen cutoff level of cortisol (15, 20, or 25 μg/dl).

Recent studies suggest that the use of steroids may be associated with reduced mortality in patients with severe sepsis [3] and severe CAP [4]. However, the present study failed to show any differences in prognosis of patients related either to use of steroids or the underlying cortisol levels. Such finding may be due to the study design and small sample size. Moreover, despite the favorable results of a randomized clinical trial [3] it is still controversial whether steroid replacement improves survival of critically ill patients [13, 14]. This underscores the necessity of better clinical and laboratory indicators to the understanding of the significance of plasma cortisol levels. Studying more homogeneous populations, such as patients with severe CAP, may be useful to determine the impact of each acute illness on the endocrine system. As expected, high frequencies of either ventilator-associated or community-acquired pneumonia (35–50%) have been observed in studies reporting improved survival [3], organ failure [3, 15], and circulating inflammatory mediators [16] in patients with severe sepsis and adrenal insufficiency treated with hydrocortisone. The high prevalence of adrenocortical insufficiency in patients with severe CAP and the high prevalence of patients with pulmonary infections enrolled in the studies that have evaluated steroid use in severe sepsis raise the question of underlying reasons for the benefits of the use of hydrocortisone for severe CAP. Monton and coworkers [17] demonstrated that glucocorticoids decrease systemic and lung inflammatory responses in mechanically ventilated patients with severe pneumonia receiving antimicrobial treatment. Confalonieri and coworkers [4] justify the clinical improvement based on possible immunomodulatory effects of the steroid infusion, thus hastening the development of acute lung injury and multiorgan failure. However, the authors' arguments are not based on the measurement of classical surrogate markers of systemic or lung inflammation such as interleukin 6 or 8, and adrenal function tests were not performed in the study's population. Therefore it can be speculated whether they were not merely treating adrenal insufficiency in severe sepsis of pulmonary origin.

As reported above, the main potential limitations of our study are its retrospective design and on the criteria used for the diagnosis of adrenal insufficiency, as the evaluation of adrenal response to the corticotropin test or free cortisol measurement were not performed. It is widely recognized that decreased amounts of cortisol-binding proteins are related to free cortisol concentrations during critical illness [18]. However, differences between albumin levels of patients with and without adrenal insufficiency or, conversely, between cortisol levels of patients with and without hypoalbuminemia were not significant in the present study.

In conclusion, the prevalence of relatively low levels of cortisol is high in patients with severe CAP. Such finding indicates that this selected population of patients with sepsis deserves to be prospectively studied in terms of adrenal function including corticotropin test or measurement of free cortisol and sequential evaluation of proinflammatory cytokines for a better understanding of the possible benefits of steroid replacement.

Acknowledgements. This work was performed at the Intensive Care Unit-Hospital Barra D'or, Rio de Janeiro, Brazil. Financial support was provided by institutional departmental funds.

References

1. Annane D, Bellissant E, Cavaillon JM (2005) Septic shock. Lancet 365:63–78
2. Keh D, Sprung CL (2004) Use of corticosteroid therapy in patients with sepsis and septic shock: an evidence-based review. Crit Care Med 32:527–533
3. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E (2002) Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288:862–871
4. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, Della Porta R, Giorgio C, Blasi F, Umberger R, Meduri GU (2005) Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med 171:242–248
5. Perla D, Marmorston J (1940) Suprarenal cortical hormone and salt in the treatment of pneumonia and other severe infections. Endocrinology 27:367–374
6. Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE (1981) APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med 9:591–597
7. Vincent JL, Moreno R, Takala J, Wilatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijy LG (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22:707–710
8. British Thoracic Society (2001) Guidelines for the management of community acquired pneumonia in adults. Thorax 56:1–64
9. American Thoracic Society (1993) Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. Am Rev Respir Dis 148:1418–1426
10. Annane D (2003) Time for a consensus definition of corticosteroid insufficiency in critically ill patients. Crit Care Med 31:1868–1869
11. Marik PE, Zaloga GP (2003) Adrenal insufficiency during septic shock. Crit Care Med 31:141–145
12. Marik PE, Gayowski T, Starzl TE (2005) The hepatoadrenal syndrome: a common yet unrecognized clinical condition. Crit Care Med 33:1254–1259
13. Rady MY, Johnson DJ, Patel B, Larson J, Helmers R (2005) Cortisol levels and corticosteroid administration fail to predict mortality in critical illness: the confounding effects of organ dysfunction and sex. Arch Surg 140:661–668
14. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y (2004) Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. BMJ 329:480
15. 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
16. Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, Volk HD, Doecke WD, Falke KJ, Gerlach H (2003) Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. Am J Respir Crit Care Med 167:512–520
17. Monton C, Ewig S, Torres A, El-Ebiary M, Filella X, Rano A, Xaubet A (1999) Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. Eur Respir J 14:218–220
18. Hamrahian AH, Oseni TS, Arafah BM (2004) Measurements of serum free cortisol in critically ill patients. N Engl J Med 350:1629–1638