

Adrenal Insufficiency in Meningococcal Sepsis: Bioavailable Cortisol Levels and Impact of Interleukin-6 Levels and Intubation with Etomidate on Adrenal Function and Mortality

Marieke den Brinker, Koen F. M. Joosten, Olivia Liem, Frank H. de Jong, Wim C. J. Hop, Jan A. Hazelzet, Marije van Dijk, and Anita C. S. Hokken-Koelega

Department of Pediatrics, Divisions of Endocrinology (M.d.B., O.L., M.v.D., A.C.S.H.-K.) and Pediatric Intensive Care (M.d.B., K.F.M.J., J.A.H.), Erasmus Medical Center–Sophia Children’s Hospital, Departments of Internal Medicine (F.H.d.J.) and Epidemiology and Biostatistics (W.C.J.H.), Erasmus Medical Center, Rotterdam, The Netherlands

Context: Adequate adrenal function is pivotal to survive meningococcal sepsis.

Objectives: The objective of the study was to evaluate adrenocortical function in meningococcal disease.

Design: This was an observational cohort study.

Setting: The study was conducted at a university-affiliated pediatric intensive care unit.

Patients: Sixty children with meningococcal sepsis or septic shock participated in the study.

Main Outcome Measures: The differences in adrenal function between nonsurvivors (n = 8), shock survivors (n = 43), and sepsis survivors (n = 9) on pediatric intensive care unit admission were measured.

Results: Nonsurvivors had significantly lower median cortisol to ACTH ratio than shock survivors and sepsis survivors. Because cortisol binding globulin and albumin levels did not significantly differ

among the groups, bioavailable cortisol levels were also significantly lower in nonsurvivors than sepsis survivors. Nonsurvivors had significantly lower cortisol to 11-deoxycortisol ratios but not lower 11-deoxycortisol to 17-hydroxyprogesterone ratios than survivors. Using multiple regression analysis, decreased cortisol to ACTH ratio was significantly related to higher IL-6 levels and intubation with etomidate (one single bolus), whereas decreased cortisol to 11-deoxycortisol ratio was significantly related only to intubation with etomidate. Aldosterone levels tended to be higher in nonsurvivors than shock survivors, whereas plasma renin activity did not significantly differ.

Conclusions: Our study shows that the most severely ill children with septic shock had signs of adrenal insufficiency. Bioavailable cortisol levels were not more informative on adrenal function than total cortisol levels. Besides disease severity, one single bolus of etomidate during intubation was related to decreased adrenal function and 11 β -hydroxylase activity. Decreased adrenal function was not related to decreased 21-hydroxylase activity. Based on our results, it seems of vital importance to take considerable caution using etomidate and consider combining its administration with glucocorticoids during intubation of children with septic shock. (*J Clin Endocrinol Metab* 90: 5110–5117, 2005)

DESPITE ADVANCES IN management and therapy, the mortality rate of children with shock due to meningococcal disease continues to be considerable (1–4). Stimulation of the hypothalamic-pituitary adrenal axis is one of the most important hormonal reactions to critical illness. Cortisol has a vital supportive role in the maintenance of vascular tone, endothelial and vascular integrity, and the distribution of total body water (5). In previously reported pilot studies (6, 7), we showed that children dying from meningococcal septic shock had relatively low cortisol levels and extremely high ACTH levels.

It is generally believed that the biological activity of cortisol depends on the free fraction of the hormone, especially

the fraction not bound to corticosteroid binding globulin (CBG), the bioavailable cortisol. Because CBG is the most important transport protein for cortisol, serum levels of cortisol may vary with CBG levels (8). Several authors demonstrated higher calculated or measured bioavailable cortisol levels during critical illness in adults than would have been expected on the basis of total cortisol levels, especially during the acute phase of critical illness (9–12). To our knowledge these data do not exist for acutely ill children.

Reduced activity of adrenal steroidogenic enzymes might lead to adrenal insufficiency in children with meningococcal sepsis. During sepsis, adrenal steroidogenic enzyme function might be liable to circulating endotoxins and/or cytokines, medication, or more intrinsically to polymorphisms. Mild forms of a decreased 21-hydroxylase function would become obvious only during extremely stressful conditions, such as sepsis, and would lead to lower cortisol levels and increased levels of its upstream precursor: 17-hydroxyprogesterone (17-OHP). The anesthetic drug etomidate is known to inhibit adrenal function by impeding mainly the enzyme 11 β -hydroxylase. For this reason, etomidate has been withdrawn

First Published Online June 28, 2005

Abbreviations: CBG, Corticosteroid binding globulin; CRP, C-reactive protein; 17-OHP, 17-hydroxyprogesterone; PICU, pediatric intensive care unit; PRISM, Pediatric Risk of Mortality II; SOFA, Sepsis-Related Organ Failure Assessment.

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

from long-term sedation regimens. Etomidate, however, is still a first-line anesthetic agent in the setting of rapid sequence intubation, in which one single bolus is used. This use of one single bolus is assumed to give only transient, clinically nonrelevant hormonal changes (13, 14).

In addition, adrenal insufficiency associated with meningococcal sepsis may also include functional loss of the zona glomerulosa and defects in the renin-mineralocorticoid axis may thereby adversely affect cardiovascular homeostasis and thus outcome. Hyperrenemic hypoaldosteronism has been reported in critically ill adults (15), whereas lower plasma aldosterone concentrations have been reported in children with meningococcal sepsis, compared with other critically ill children (16). Data concerning the renin-mineralocorticoid axis in relation to outcome in children with meningococcal sepsis are, however, lacking.

In this study, our aim was to evaluate whether low total cortisol levels correspond with low bioavailable cortisol levels in children with meningococcal sepsis. In addition we aimed to assess whether reduced 21-hydroxylase or 11 β -hydroxylase functions might underlie the adrenal insufficiency in children dying from meningococcal disease. Furthermore, we wanted to determine which factors were associated with adrenal insufficiency and mortality. We therefore evaluated adrenocortical function in a large group of children with meningococcal sepsis on admission to the pediatric intensive care unit (PICU).

Patients and Methods

Patients

The group consisted of 69 previously healthy children admitted to the PICU of Erasmus Medical Center–Sophia Children's Hospital between October 1997 and October 1999 and between October 2001 and January 2004, with a clinical picture of meningococcal sepsis, defined as sepsis with petechiae/purpura. Sepsis was defined as temperature lower than 36.0 C higher than 38.5 C with tachycardia and tachypnea. In addition, children were assigned to have septic shock if they also had persistent hypotension or evidence of poor end-organ perfusion, as described previously (6, 17). Nine children who received corticosteroid therapy for suspected adrenal insufficiency before admission were excluded. It is important to note that administration of glucocorticoids during septic shock or after a single bolus of etomidate in the setting of rapid sequence intubation is not a routine procedure in The Netherlands. The medical ethics committee approved the study, and written informed consent was obtained from the parents or legal representatives of each patient before their participation in the study. Pilot data on total cortisol and ACTH levels of 27 children included between October 1997 and October 1999 have been published previously (6, 7).

Concomitant therapy and caloric intake

Concomitant therapy on admission included antibiotics (Cefotaxime; Sanofi-Aventis, Gouda, The Netherlands) and administration of fluids in all 60 children and inotropics in 51 children. At a median of 2 h 40 min before admission, 31 children were mechanically ventilated, of whom 23 had been intubated with one bolus of etomidate (median dose, 0.29 mg/kg) and eight with combinations of opiate agonists, propofol, ketamine, or midazolam. Mechanically ventilated children were sedated with benzodiazepines and/or morphine. On admission, patients received glucose iv at a rate of 4–6 mg/kg·min. They did not receive enteral or parenteral feeding until the second day.

Clinical parameters

Disease severity was determined using the Pediatric Risk of Mortality II (PRISM) score (6, 18) and the Sepsis-Related Organ Failure Assessment

(SOFA) score (19) and by measuring levels of established biomarkers, such as plasma IL-6, arterial lactate, and serum C-reactive protein (CRP). We recorded the interval between appearance of first petechia and PICU admission, respiratory support, drug use, blood pressure, and outcome. Blood pressure SD scores (Z-scores) were calculated based on published reference data (20).

Collection of blood samples

Arterial blood samples were obtained as soon as possible after admission. After clotting and centrifugation, serum and plasma were stored at –80 C until determination of CBG, 17-OHP, 11-deoxycortisol, and IL-6. All other laboratory parameters were determined immediately. The accuracy of cortisol and ACTH assays was guaranteed by continuously monitoring of intra- and interassay variabilities by estimating hormone concentrations in three serum pools in every assay. Whenever a pool was exhausted, samples from a new pool were estimated in parallel for at least five assays. A certified clinical chemistry laboratory (ISO 17025 and 9001) determined the other parameters.

Hormone analyses

Serum cortisol concentrations were measured by a competitive luminescence immunoassay (Immulite 2000; Diagnostic Products Corp., Los Angeles, CA) and plasma ACTH concentrations by an immunoradiometric assay (BioInternational, Gif sur Yvette, France). Because reference values of cortisol and ACTH for critical illness do not exist, we depicted nonstressed reference values for ACTH (<11 pmol/liter) and cortisol (between 200 and 800 nmol/liter at 0800 h) in tables and figures as a point of reference. 17-OHP was determined by an in-house RIA as described earlier (21). Values of 17-OHP below the assay's detection limit were set at the detection limit of 0.1 nmol/liter. Nonstressed reference values for 17-OHP were less than 5 nmol/liter for children younger than 12 yr of age and less than 10 nmol/liter for older children. Serum 11-deoxycortisol levels were obtained on admission and determined by RIA (22), using an antiserum from ICN Biomedicals (Costa Mesa, CA). Nonstressed reference values for 11-deoxycortisol were less than 50 nmol/liter. Serum CBG concentrations were measured by RIA (BioSource, Nivelles, Belgium). Because reference values for CBG were not available for children, we used reference values for adult men (between 442 and 1596 nmol/liter), except for girls 12 yr and older for whom reference values for women (between 615 and 2865 nmol/liter) were used. The within- and between-assay variation coefficients for the assays of cortisol, ACTH, and 17-OHP were less than 7% and for CBG and 11-deoxycortisol less than 14%.

We calculated bioavailable cortisol, which represents the non-CBG-bound fraction, from total cortisol, CBG, and albumin levels using the formula based on binding equilibrium as described earlier (23, 24) with the association constants of CBG and albumin for cortisol (25).

Plasma aldosterone levels were determined by RIA (Diagnostic Products Corp.) and plasma renin activity by an in-house assay, as described elsewhere (26).

Other laboratory analyses

Arterial lactate and glucose were measured on a blood gas analyzer (ABL 625; Radiometer, Copenhagen, Denmark). Serum CRP was measured by an immunoturbidimetric assay, and serum albumin was measured by a bromocresol purple method, both on a Hitachi 912 analyzer (Roche Diagnostics, Mannheim, Germany). The reference values were less than 2.0 mmol/liter for lactate, less than 10 mg/liter for CRP, 2.6–11.0 mmol/liter for glucose, and 35–50 g/liter for albumin. Plasma IL-6 levels were analyzed using an ELISA (Sanquin, Amsterdam, The Netherlands).

Statistics

The results are expressed as medians unless specified otherwise. We used Mann-Whitney *U*, χ^2 , or Fischer's exact test for group comparison and Spearman's correlation coefficients (*r*) to evaluate the relationship between different parameters. Multiple linear regression analysis was used to evaluate the relationships between various parameters and

cortisol to ACTH and cortisol to 11-deoxycortisol ratios (both log transformed). Two-tailed $P < 0.05$ was considered statistically significant.

Results

Clinical parameters

The study group consisted of 60 children, 37 boys and 23 girls, admitted to the PICU without receiving glucocorticoid therapy before study enrollment. All children showed a clinical picture of meningococcal sepsis and blood cultures revealed *Neisseria meningitidis* in 50 of them. Children were divided according to presence of shock and survival into the following disease severity groups: (shock) nonsurvivors ($n = 8$), shock survivors ($n = 43$), and sepsis survivors ($n = 9$). Nonsurvivors were significantly younger and had significantly shorter time from first petechia to admission than survivors (Table 1). Parameters of disease severity, such as PRISM and SOFA score, plasma IL-6, and arterial lactate levels were significantly higher in nonsurvivors, compared with survivors, and in shock survivors, compared with sepsis survivors, whereas CRP levels were significantly lower in nonsurvivors, compared with survivors. Arterial glucose levels were significantly lower in nonsurvivors, compared with survivors. Nonsurvivors were more often mechanically ventilated and had been more often intubated with etomidate than survivors, and shock survivors more often than sepsis survivors. Nonsurvivors and shock survivors received more often inotropic support than sepsis survivors, whereas systolic and diastolic blood pressure SD scores did not significantly differ between the groups (data not shown).

Cortisol and ACTH levels

Total cortisol levels did not increase with increasing disease severity: nonsurvivors had significantly lower median serum cortisol levels than shock survivors as well as sepsis survivors, and shock survivors had significantly lower cortisol levels than sepsis survivors (Table 2 and Fig. 1). ACTH levels were significantly higher in nonsurvivors, compared with shock survivors and sepsis survivors. As a result, nonsurvivors had significantly lower median total cortisol to ACTH ratios, compared with survivors, and shock survivors had significantly lower cortisol to ACTH ratios than sepsis survivors. Parameters of disease severity, such as PRISM and SOFA score, IL-6, and lactate levels, correlated positively

with ACTH levels and negatively with serum cortisol levels as well as cortisol to ACTH ratios (Table 3). Arterial glucose levels correlated negatively with ACTH levels and positively with cortisol to ACTH ratio. Age and time from first petechia to admission did not correlate with cortisol levels, ACTH levels, or their ratio (data not shown).

CBG and bioavailable cortisol levels

On admission, serum CBG levels ranged from 223 to 1793 nmol/liter. CBG levels were within the normal range in the vast majority of children (86%), elevated in one girl (1.3 yr of age), and decreased in seven children, of which one girl was older than 12 yr. Serum CBG and albumin levels did not significantly differ among nonsurvivors, shock survivors, and sepsis survivors (Table 2), and CBG levels did not correlate with parameters of disease severity (Table 3). Median bioavailable cortisol levels were significantly lower in nonsurvivors and shock survivors, compared with sepsis survivors (Table 2 and Fig. 1) and correlated negatively with parameters of disease severity (Table 3) and positively with CRP levels but not with age or time from first petechia to admission.

17-OHP and 11-deoxycortisol levels and ratios with cortisol

On admission, serum 17-OHP ranged from values below the detection limit of 0.1 to 28.9 nmol/liter and serum 11-deoxycortisol levels ranged from 7 to 468 nmol/liter. Nonsurvivors had significantly lower 17-OHP levels than survivors, whereas median 11-deoxycortisol levels did not significantly differ between the groups (Table 2). Nonsurvivors had significantly higher 11-deoxycortisol to 17-OHP ratios and significantly lower cortisol to 11-deoxycortisol ratios than survivors, whereas these ratios did not significantly differ between all shock survivors and sepsis survivors and also between shock survivors and sepsis survivors who did not receive etomidate (data not shown). Most parameters of disease severity correlated positively with 11-deoxycortisol to 17-OHP ratios and negatively with cortisol to 11-deoxycortisol ratios but not with serum 17-OHP and 11-deoxycortisol levels (Table 3). Arterial glucose levels correlated negatively with 11-deoxycortisol levels and 11-deoxycortisol to 17-OHP ratios and positively with cortisol to

TABLE 1. Patients' characteristics on admission, divided in nonsurvivors, shock survivors, and sepsis survivors

Variables	Nonsurvivors (n = 8)	Shock survivors (n = 43)	Sepsis survivors (n = 9)
Male gender (%)	6 (75)	26 (60)	5 (56)
Age (yr)	0.8 (0.5–1.9) ^a	5.0 (2.1–10.2)	4.8 (2.7–10.9)
Time of first petechia, admission (h)	5.3 (3.8–7.6) ^a	7.3 (6.2–9.8)	7.6 (5.7–9.0)
PRISM score	34 (26–36) ^a	20 (16–27) ^b	9 (8–12)
SOFA score	16 (14–19) ^a	9 (7–11) ^b	2 (2–4)
IL-6 × 10 ³ (pg/ml)	1195.5 (853.1–1776.7) ^a	45.9 (4.8–126.9) ^b	0.4 (0.1–5.6)
Lactate (mmol/liter)	7.3 (5.9–8.7) ^a	3.9 (2.6–5.4) ^b	2.1 (1.4–2.5)
CRP (mg/liter)	31 (22–36) ^a	85 (58–131)	75 (64–215)
Glucose (mmol/liter)	3.9 (2.5–6.5) ^a	6.9 (5.6–9.1)	8.2 (7.1–9.7)
Mechanical ventilation (%)	8 (100) ^a	23 (53) ^b	0 (0)
Intubated with etomidate (%)	7 (88) ^a	16 (37) ^b	0 (0)
Inotropic support (%)	8 (100) ^b	41 (95) ^b	2 (22)

All values are expressed as median (25th to 75th percentile). For reference values, see *Patients and Methods*.

^a Significantly different, compared with all survivors, $P < 0.05$.

^b Significantly different, compared with sepsis survivors, $P < 0.05$.

TABLE 2. Endocrine levels on admission, divided in nonsurvivors, shock survivors, and sepsis survivors

Variables	Shock nonsurvivors (n = 8)	Shock survivors (n = 43)	Sepsis survivors (n = 9)
Total cortisol (nmol/liter)	615 (490–790) ^a	953 (696–1160) ^b	1276 (1044–1895)
ACTH (pmol/liter)	274.1 (164.4–647.1) ^a	49.5 (13.4–109.7)	5.9 (3.8–70.8)
Total cortisol to ACTH ratio ($\times 10^3$)	2.6 (0.8–4.5) ^a	21.2 (5.4–90.3) ^b	195.3 (18.2–330.0)
CBG (nmol/liter)	892 (466–1175)	700 (552–1108)	831 (668–1223)
Albumin (g/liter)	40 (28–41)	33 (27–39)	34 (31–39)
Bioavailable cortisol (nmol/liter)	106 (30–220) ^b	173 (59–532) ^b	511 (356–843)
17-OHP (nmol/liter)	2.8 (1.9–6.5) ^a	8.7 (3.9–10.3)	11.2 (3.4–15.3)
11-deoxycortisol (nmol/liter)	143 (102–176)	70 (53–167)	73 (44–127)
11-deoxycortisol to 17-OHP ratio	48 (17–72) ^a	10 (7–29)	13 (6–17)
Cortisol to 11-deoxycortisol ratio	4.1 (3.1–4.8) ^a	16.0 (3.9–21.3)	17.3 (10.4–24.9)
Aldosterone (pg/ml)	569 (320–803)	296 (169–427)	269 (216–1475)
Plasma renin activity (ng Ang I/ml-h)	15.9 (5.2–37.4)	19.5 (9.3–34.4)	19.1 (9.7–76.9)

All values are expressed as median (25th to 75th percentile). Ang I, Angiotensin I. For reference values, see *Patients and Methods*.

^a Significantly different, compared with all survivors, $P < 0.05$.

^b Significantly different, compared with sepsis-survivors, $P < 0.05$.

11-deoxycortisol ratios. Both serum 17-OHP and 11-deoxycortisol levels did not correlate with age and did not differ between girls and boys. Plasma ACTH levels and cortisol to ACTH ratios correlated significantly with 11-deoxycortisol levels ($r = 0.44$ and $r = -0.39$, respectively), whereas 17-OHP levels did not (data not shown).

Aldosterone levels and plasma renin activity

On admission, plasma aldosterone levels ranged from 129 to 1867 pg/ml and plasma renin activity from 3.3 to 97.2 ng angiotensin I per milliliter per hour. Aldosterone levels tended to be higher in nonsurvivors, compared with shock survivors ($P = 0.057$) but did not significantly differ between shock survivors and sepsis survivors. Plasma renin activity did not significantly differ among nonsurvivors, shock survivors, and sepsis survivors. Aldosterone levels correlated significantly with age ($r = -0.69$) and IL-6 levels ($r = 0.33$) but not with other parameters of disease severity (Table 3), plasma renin activity, or ACTH levels (data not shown). Plasma renin activity correlated significantly with systolic blood pressure SD score ($r = -0.39$) but not with diastolic blood pressure SD score, any parameter of disease severity, or age. Aldosterone levels and plasma renin activity did not significantly differ between children who received inotropics and those who did not.

Multivariate analysis

In univariate regression analyses, the cortisol to ACTH ratio was significantly related to IL-6, CRP, 17-OHP, 11-deoxycortisol levels, age, mechanical ventilation, and intubation with etomidate but not to gender and time from first petechia to admission. Using multiple regression analysis, we found cortisol to ACTH ratios to be significantly related to IL-6 levels and intubation with etomidate before admission. These two variables in combination explained 65% of the variation in cortisol to ACTH ratio on admission, whereas IL-6 alone explained 45%. The cortisol to ACTH ratios decreased by 19% for every doubling of IL-6 levels and by 83% when etomidate was administered (Fig. 2). In contrast, analyzing the relation between cortisol to ACTH ratios and IL-6 levels, we found no significant difference between children who were intubated without etomidate and those who were not intubated (ANCOVA, $P = 0.774$). Children who were

intubated on admission, independently of intubation with etomidate, had significantly higher disease severity parameters, such as PRISM, SOFA, IL-6, and lactate levels, than children who were not intubated.

In univariate regression analyses, the cortisol to 11-deoxycortisol ratio was significantly related to IL-6, CRP, ACTH levels, mechanical ventilation, and intubation with etomidate but not to age, gender, time from first petechia to admission, or 17-OHP levels. Using multiple regression analysis, we found only intubation with etomidate to be significantly predictive for cortisol to 11-deoxycortisol ratios, explaining 78% of the variation in cortisol to 11-deoxycortisol ratio on admission. The mean decrease of cortisol to 11-deoxycortisol ratios was 84% when children were intubated with etomidate (Fig. 3).

Discussion

In this study we found that the most severely ill children with meningococcal septic shock had signs of adrenal insufficiency on PICU admission, indicated by low cortisol and very high ACTH levels. Low total cortisol levels proved to correspond with low bioavailable cortisol. Serum CBG levels were normal in the vast majority of the children. We did not find signs of a reduced 21-hydroxylase activity because the 11-deoxycortisol to 17-OHP ratio was not reduced. We found, however, a reduction in the cortisol to 11-deoxycortisol ratio, indicating that the 11 β -hydroxylase activity was significantly reduced, particularly in the nonsurvivors. Nonsurvivors had significantly reduced cortisol to ACTH ratio, compared with the survivors. The cortisol to ACTH ratio was negatively related to IL-6 levels and various other disease severity scores. Using multiple regression analysis, it turned out that a decreased cortisol to ACTH ratio was significantly related to higher IL-6 levels and intubation with etomidate, whereas a lower cortisol to 11-deoxycortisol ratio was only significantly related to intubation with etomidate.

First of all, we examined whether total cortisol levels corresponded with bioavailable cortisol levels. Serum CBG and to a much lesser extent albumin are the most important serum proteins for transport of cortisol, thereby roughly determining the biologically active cortisol concentration. We found normal CBG and albumin levels in the vast majority of the children with meningococcal disease on PICU

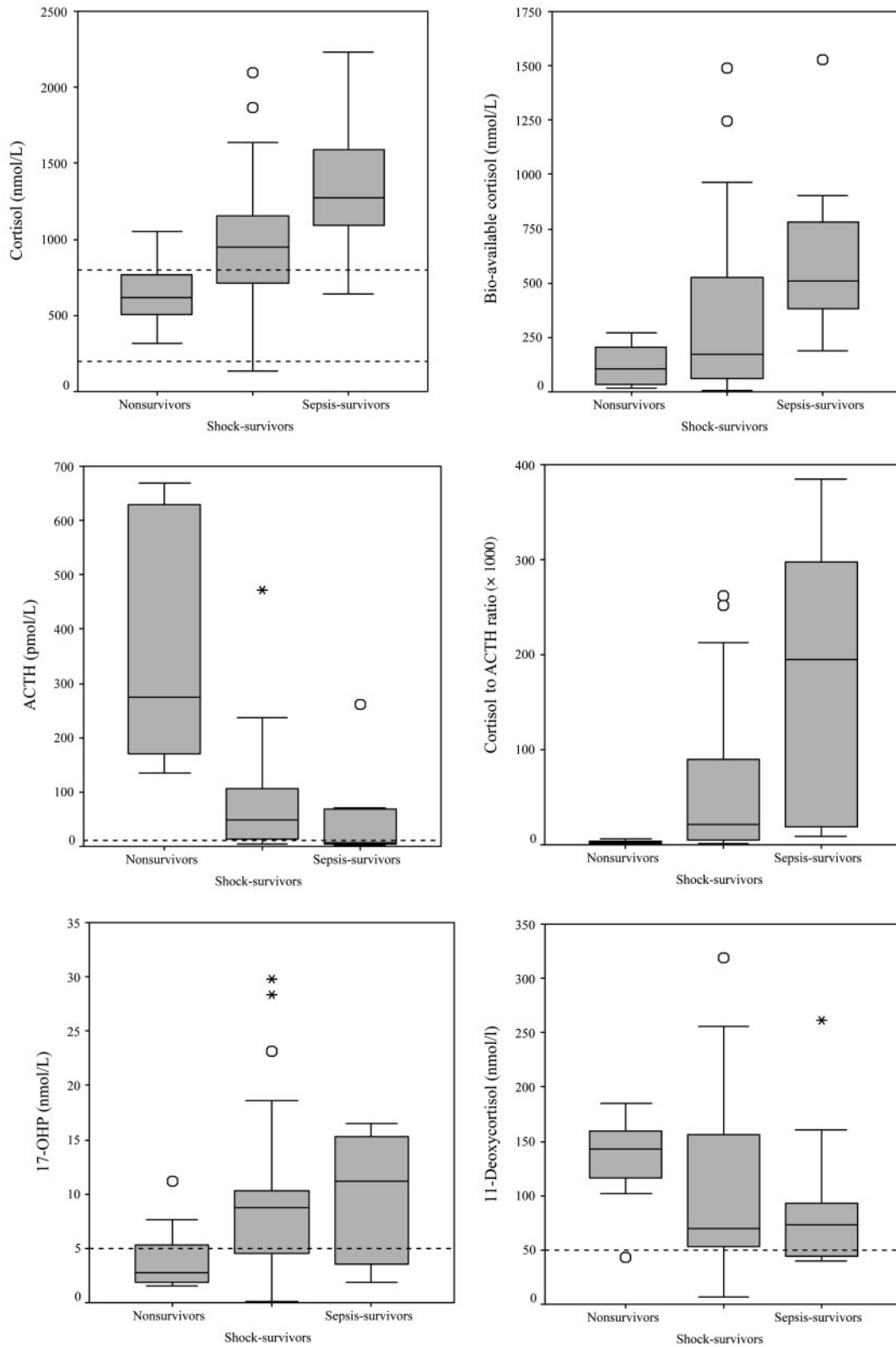


FIG. 1. Serum cortisol levels, bioavailable cortisol levels, ACTH levels, cortisol to ACTH ratios, 17-OHP levels, and 11-deoxycortisol levels on admission. Nonsurvivors are depicted in the *left box*, shock survivors in the *middle box*, and sepsis survivors in the *right box*. Box-plots indicate 25–75 percentile with the median and whiskers the range without outliers (○) and extremes (*). Reference values are *between or below the dotted lines*.

TABLE 3. Significant Spearman correlation coefficients of hormones of the hypothalamus-pituitary-adrenal axis with parameters of disease severity

	PRISM	SOFA	Lactate	IL-6	CRP	Glucose
Cortisol	-0.48	-0.59	-0.41	-0.45	0.46	—
ACTH	0.49	0.60	0.54	0.66	-0.35	-0.30
Cortisol/ACTH	-0.58	-0.70	-0.62	-0.72	0.43	0.32
CBG	—	—	—	—	—	—
Bioavailable cortisol	-0.35	-0.55	-0.41	-0.30	0.37	—
17-OHP	—	—	—	—	—	—
11-deoxycortisol	—	—	—	—	—	-0.29
11-deoxycortisol/17-OHP	—	0.38	—	0.39	—	-0.38
Cortisol/11-deoxycortisol	-0.40	-0.43	-0.35	-0.47	0.27	0.37
Cortisol/17-OHP	—	—	—	—	—	—
Aldosterone	—	—	—	0.33	—	—
Plasma renin activity	—	—	—	—	—	—

Nonsignificant correlation coefficients are represented with a dash.

admission, indicating that the low total cortisol levels do correspond with low bioavailable cortisol levels in these children. This is in contrast to studies in critically ill adults reporting decreased serum CBG and albumin levels with concomitantly elevated free cortisol fractions especially during the acute phase of critical illness (9, 10, 12). A possible explanation for this difference might be that children in our study received plasma products from healthy adult donors as volume supplementation, which might have prevented a decline in CBG levels. From our study we can conclude that bioavailable cortisol levels were not more informative on adrenal function than total cortisol levels in these children on PICU admission.

The extremely elevated ACTH levels in combination with

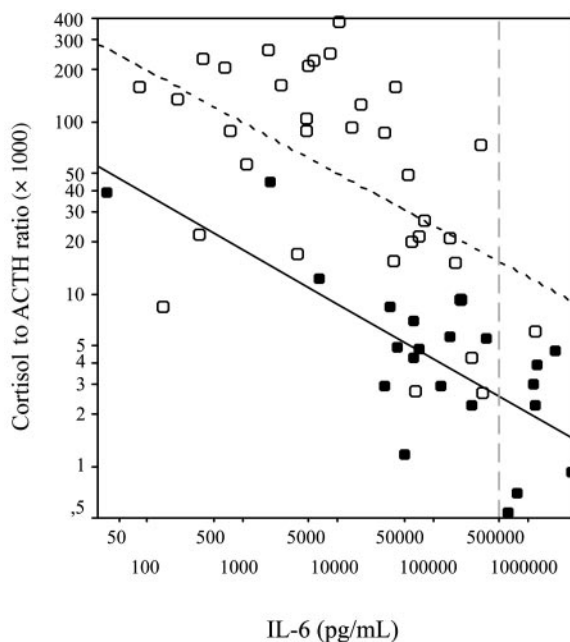


FIG. 2. Relation between cortisol to ACTH ratios and IL-6 levels, in children who received etomidate (●, continuous line) and children who did not receive etomidate (○, dotted line). After adjustment for IL-6 levels, using multiple regression, mean cortisol to ACTH ratios were significantly higher in case of etomidate use ($P < 0.001$). The vertical gray dotted line (IL-6 level of 500,000 pg/ml) discriminates survivors (left) from nonsurvivors (right).

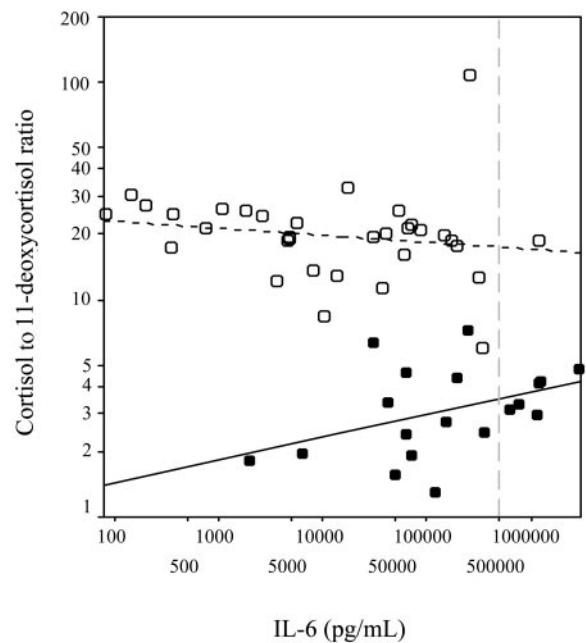


FIG. 3. The cortisol to 11-deoxycortisol ratio in relation to IL-6 levels, in children who received etomidate (●, continuous line) and children who did not receive etomidate (○, dotted line). Mean cortisol to 11-deoxycortisol ratios were significantly higher in case of etomidate use ($P < 0.001$). The vertical gray dotted line (IL-6 level of 500,000 pg/ml) discriminates survivors (left) from nonsurvivors (right).

the decreased cortisol levels in nonsurvivors represent an inadequate adrenal response. We therefore investigated whether the enzymes 21-hydroxylase and 11-hydroxylase were not or less active in this condition by measuring 11-deoxycortisol to 17-OHP and cortisol to 11-deoxycortisol ratios. It turned out that with increasing disease severity there were more signs of decreased 11 β -hydroxylase activity, as depicted by lower cortisol to 11-deoxycortisol ratios, whereas we found no signs of decreased 21-hydroxylase activity. The median 11-deoxycortisol to 17-OHP ratio was significantly higher in nonsurvivors than survivors, which may have resulted from accumulation of 11-deoxycortisol levels by decreased 11 β -hydroxylase activity. In search of factors influencing adrenal function, we found, besides disease severity, mechanical ventilation and in particular intubation with one single bolus of etomidate to be significantly related to decreased adrenal function at the level of 11 β -hydroxylase. As Fig. 2 shows, IL-6 levels higher than 500,000 pg/ml was discriminating for mortality. Etomidate was found to reduce 11 β -hydroxylase activity independently of disease severity (Fig. 3).

Our study suggests that the addition of one single bolus of etomidate to the existing overwhelming immune reaction in the most severely ill children might have increased the risk for mortality. For the less severely ill children, the addition of etomidate appeared not so disastrous. It is, however, difficult to identify the relative contribution of the disease severity and the intubation with etomidate because the most severely ill children were more likely to be intubated than the less severely ill children. In our study the group of intubated children without etomidate was too small to differentiate

whether etomidate was given, depending on the disease severity. We assume, however, it was not of influence because all children were intubated in the setting of a rapid-sequence intubation. *In vitro* studies have shown that etomidate interferes with mainly two steroidogenic enzymes: the cholesterol (P450) side-chain cleavage enzyme system and 11 β -hydroxylase (21, 22, 27). Already 20 yr ago etomidate has been withdrawn from the long-term sedation regimen due to high death rates; however, it still is a first-line anesthetic agent in the setting of rapid sequence intubation, in which one single bolus is used. This use of one single bolus had been assumed to give only transient, not clinically relevant, hormonal changes (14, 28). Although our study was not designed to study the direct effect of etomidate administration on adrenal function and mortality, our data suggest that in the most severely ill children with septic shock, the risk of death might have been increased by one single bolus of etomidate during intubation. This should be further investigated.

Our present study indicates that adrenal insufficiency should be considered in all children with severe sepsis and septic shock but particularly so when they received a bolus of etomidate during intubation. Based on our results and awaiting the final results future studies, it seems of vital importance to take considerable caution using etomidate and consider combining its administration with glucocorticoids during intubation of children with septic shock.

Various other mechanisms might be important in the pathogenesis of relative adrenal insufficiency during sepsis, such as impairment of enzymes of the steroidogenic pathway before 21-hydroxylase, ACTH receptor insensitivity, decreased levels of cholesterol, decreased (adrenal) blood flow during severe shock, and adrenal hemorrhage. All these factors might adversely influence cortisol production in the most severely ill children (29–32).

In our study, aldosterone levels tended to be higher in nonsurvivors, compared with shock survivors and correlated positively but weakly with IL-6 levels. However, because aldosterone levels were inversely correlated with age, this trend was apparently influenced by the younger age of nonsurvivors, compared with survivors. Plasma renin activity related negatively to age-matched systolic blood pressure values, suggesting an adequately renin response. However, plasma renin activity did not correlate with aldosterone levels, suggesting an inadequate aldosterone response.

In summary, our study shows that the most severely ill children with meningococcal septic shock had signs of adrenal insufficiency on PICU admission. Bioavailable cortisol levels were not more informative on adrenal function than total cortisol levels. Decreased adrenal function was strongly inversely related to IL-6 levels and at least partly to a decreased 11 β -hydroxylase activity but not to a decreased 21-hydroxylase. In addition to IL-6 levels, one single bolus of etomidate during intubation was related to a decreased adrenal function and 11 β -hydroxylase activity. Based on our results, it seems of vital importance to take considerable caution using etomidate during intubation of children with septic shock and consider combining its administration with glucocorticoids.

Acknowledgments

We thank M. Maliepaard (research nurse) for her technical assistance, C. L. Vermont, M.D., Ph.D., and E. D. de Kleijn, M.D., Ph.D., and their colleagues as well as E. M. N. Bannink, R. D. van Beek, V. H. Boonstra, M. van Dijk, D. A. M. Festen, D. van der Kaay, and A. S. Slingerland (all M.D.s) for assisting to collect samples on weekends and the nursing staff of the pediatric intensive care for their support. We also thank F. Boomsma, Ph.D., for determining aldosterone levels and plasma renin activity.

Received May 18, 2005. Accepted June 22, 2005.

Address all correspondence and requests for reprints to: Marieke den Brinker, M.D., Department of Pediatrics, Division of Endocrinology and Division of Pediatric Intensive Care, Erasmus Medical Center–Sophia Children's Hospital, P.O. Box 2060, 3000 CB Rotterdam, The Netherlands. E-mail: m.denbrinker@erasmusmc.nl.

M.d.B. was supported by a grant from Pfizer.

This was an investigator-initiated project.

References

- Mok Q, Butt W 1996 The outcome of children admitted to intensive care with meningococcal septicemia. *Intensive Care Med* 22:259–263
- Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM 2001 Meningococcal disease. *N Engl J Med* 344:1378–1388
- Friedman G, Silva E, Vincent JL 1998 Has the mortality of septic shock changed with time. *Crit Care Med* 26:2078–2086
- Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM 2004 Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Intensive Care Med* 30:536–555
- Lamberts SW, Bruining HA, de Jong FH 1997 Corticosteroid therapy in severe illness. *N Engl J Med* 337:1285–1292
- Joosten KF, de Kleijn ED, Westerterp M, de Hoog M, Eijck FC, Hop WCJ, Voort EV, Hazelzet JA, Hokken-Koelega AC 2000 Endocrine and metabolic responses in children with meningococcal sepsis: striking differences between survivors and nonsurvivors. *J Clin Endocrinol Metab* 85:3746–3753
- De Kleijn ED, Joosten KF, Van Rijn B, Westerterp M, De Groot R, Hokken-Koelega AC, Hazelzet JA 2002 Low serum cortisol in combination with high adrenocorticotropic hormone concentrations are associated with poor outcome in children with severe meningococcal disease. *Pediatr Infect Dis J* 21:330–336
- Rosner W 1990 The functions of corticosteroid-binding globulin and sex hormone-binding globulin: recent advances. *Endocr Rev* 11:80–91
- Beishuizen A, Thijs LG, Vermes I 2001 Patterns of corticosteroid-binding globulin and the free cortisol index during septic shock and multitrauma. *Intensive Care Med* 27:1584–1591
- 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
- le Roux CW, Chapman GA, Kong WM, Dhillon WS, Jones J, Alagband-Zadeh J 2003 Free cortisol index is better than serum total cortisol in determining hypothalamic-pituitary-adrenal status in patients undergoing surgery. *J Clin Endocrinol Metab* 88:2045–2048
- Hamrahian AH, Oseni TS, Arafah BM 2004 Measurements of serum free cortisol in critically ill patients. *N Engl J Med* 350:1629–1638
- Jackson Jr WL 2005 Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock? a critical appraisal. *Chest* 127:1031–1038.
- Oglesby AJ 2004 Should etomidate be the induction agent of choice for rapid sequence intubation in the emergency department? *Emerg Med J* 21:655–659
- Zipser RD, Davenport MW, Martin KL, Tuck ML, Warner NE, Swinney RR, Davis CL, Horton R 1981 Hyperreninemic hypoadosteronism in the critically ill: a new entity. *J Clin Endocrinol Metab* 53:867–873
- Lichterowicz-Krynska EJ, Cole TJ, Camacho-Hubner C, Britto J, Levin M, Klein N, Aynsley-Green A 2004 Circulating aldosterone levels are unexpectedly low in children with acute meningococcal disease. *J Clin Endocrinol Metab* 89:1410–1414
- Abraham E, Matthay MA, Dinarello CA, Vincent JL, Cohen J, Opal SM, Glauser M, Parsons P, Fisher Jr CJ, Repine JE 2000 Consensus conference definitions for sepsis, septic shock, acute lung injury, and acute respiratory distress syndrome: time for a reevaluation. *Crit Care Med* 28:232–235
- Pollack MM, Ruttimann UE, Getson PR 1988 Pediatric risk of mortality (PRISM) score. *Crit Care Med* 16:1110–1116
- Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs 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

20. 1987 Report of the Second Task Force on Blood Pressure Control in Children—1987. Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, MD. *Pediatrics* 79:1–25
21. **Lamberts SW, Bons EG, Bruining HA, de Jong FH** 1987 Differential effects of the imidazole derivatives etomidate, ketoconazole and miconazole and of metyrapone on the secretion of cortisol and its precursors by human adrenocortical cells. *J Pharmacol Exp Ther* 240:259–264
22. **de Jong FH, Mallios C, Jansen C, Scheck PA, Lamberts SW** 1984 Etomidate suppresses adrenocortical function by inhibition of 11 β -hydroxylation. *J Clin Endocrinol Metab* 59:1143–1147
23. **de Ronde W, van der Schouw YT, Muller M, Grobbee DE, Gooren LJ, Pols HA, de Jong FH** 2005 Associations of sex-hormone-binding globulin (SHBG) with non-SHBG-bound levels of testosterone and estradiol in independently living men. *J Clin Endocrinol Metab* 90:157–162
24. **Sodergard R, Backstrom T, Shanbhag V, Carstensen H** 1982 Calculation of free and bound fractions of testosterone and estradiol-17 β to human plasma proteins at body temperature. *J Steroid Biochem* 16:801–810
25. **Dunn JF, Nisula BC, Rodbard D** 1981 Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. *J Clin Endocrinol Metab* 53:58–68
26. **Derkx FH, Tan-Tjong L, Wenting GJ, Boomsma F, Man in't Veld AJ, Schalekamp MA** 1983 Asynchronous changes in prorenin and renin secretion after captopril in patients with renal artery stenosis. *Hypertension* 5:244–256
27. **Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D** 1984 Inhibition of adrenal steroidogenesis by the anesthetic etomidate. *N Engl J Med* 310:1415–1421
28. **Annane D** 2005 ICU physicians should abandon the use of etomidate! *Intensive Care Med* 31:325–326
29. **Catalano RD, Parameswaran V, Ramachandran J, Trunkey DD** 1984 Mechanisms of adrenocortical depression during *Escherichia coli* shock. *Arch Surg* 119:145–150
30. **Jaattela M, Ilvesmaki V, Voutilainen R, Stenman UH, Saksela E** 1991 Tumor necrosis factor as a potent inhibitor of adrenocorticotropin-induced cortisol production and steroidogenic P450 enzyme gene expression in cultured human fetal adrenal cells. *Endocrinology* 128:623–629
31. **van der Voort PH, Gerritsen RT, Bakker AJ, Boerma EC, Kuiper MA, de Heide L** 2003 HDL-cholesterol level and cortisol response to synacthen in critically ill patients. *Intensive Care Med* 29:2199–2203
32. **Vermont CL, den Brinker M, Kakeci N, de Kleijn ED, De Rijke YB, De Groot R, Hazelzet JA** 2005 Serum lipids and disease severity in children with severe meningococcal sepsis. *Crit Care Med* 33:1610–1615

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.