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BRIEF REPORT

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One single dose of etomidate negatively influences adrenocortical performance for at least 24 h in children with meningococcal sepsis

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Abstract *Objective:* To investigate the effect of one single bolus of etomidate used for intubation on adrenal function in children with meningococcal sepsis. *Design:* Retrospective study conducted between 1997 and 2004. *Setting:* University-affiliated paediatric intensive care unit (PICU). *Patients and participants:* Sixty children admitted to the PICU with meningococcal sepsis, not treated with steroids. *Interventions:* Adrenal hormone concentrations were determined as soon as possible after PICU admission, and after 12 h and 24 h. To assess disease severity, PRISM score and selected laboratory parameters were determined. *Measurements and main results:* On admission, before blood was drawn, 23 children had been intubated with etomidate, 8 without etomidate and 29 were not intubated. Children who were intubated had significantly higher disease severity parameters than those not intubated, whereas none of these parameters significantly differed between children intubated with or without etomidate. Children who received etomidate had significantly lower cortisol, higher ACTH and higher 11-deoxycortisol levels than those who did not receive etomidate. Arterial glucose levels were significantly lower in children who were intubated with etomidate than in non-intubated children. When children were intubated with etomidate, cortisol levels were 3.2 times lower for comparable 11-deoxycortisol levels. Eight children died, seven of whom had received etomidate. Within 24 h cortisol/ACTH and cortisol/11-deoxycortisol ratios increased significantly in children who received etomidate, but not in children who did not, resulting in comparable cortisol/ACTH ratios with still significantly lowered cortisol/11-deoxycortisol ratios 24 h after admission. *Conclusions:* Our data imply that even one single bolus of etomidate negatively influences adrenal function for at least 24 h. It might therefore increase risk of death.

Keywords Adrenal insufficiency · Etomidate · Critical illness · Meningococcal disease · Child

Introduction

Stimulation of the hypothalamic-pituitary adrenal axis is one of the most important hormonal reactions to critical illness [1]. The anaesthetic drug etomidate is known to inhibit adrenal function by mainly impeding the enzyme 11β-hydroxylase, the last step in the biosynthesis of cortisol, resulting in increased levels of 11-deoxycortisol in relation to cortisol [2] (Fig. 1). Since long-term etomidate use has resulted in increased mortality, etomidate has been withdrawn from long-term sedation regimens [3]. Etomidate, however, remained a first-line anaesthetic agent in the setting of rapid sequence intubation, because it has a favourable cardiopulmonary profile. One single

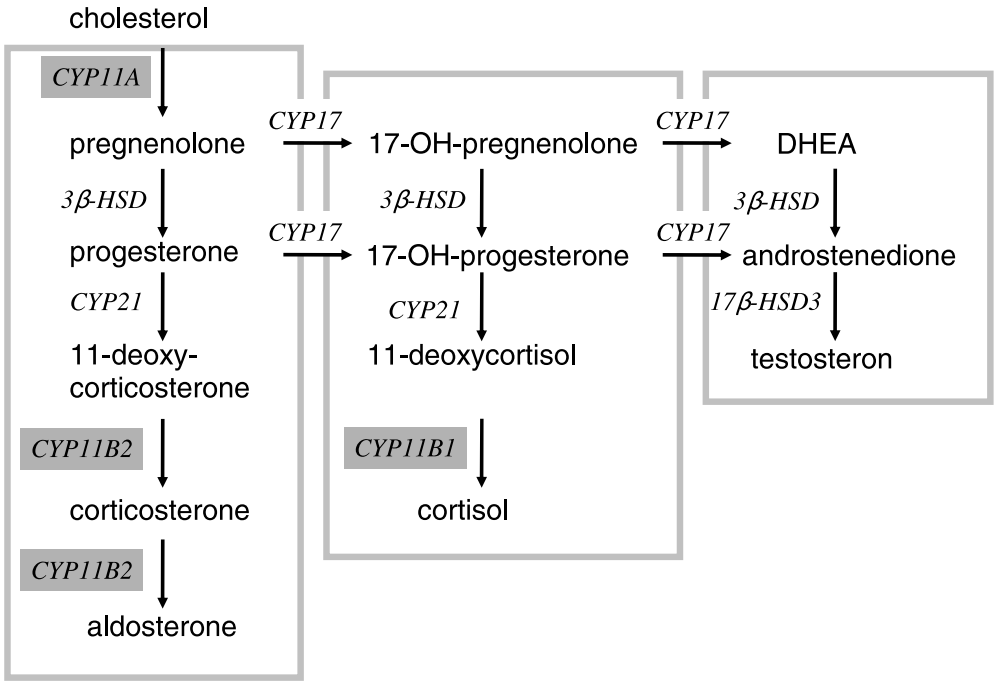

Fig. 1 A schematic representation of steroidogenesis in the human adrenal gland and the effect of etomidate. Etomidate inhibits 11β-hydroxylase (*CYP11B1*), 11β- and 18-hydroxylase (*CYP11B2*) and cholesterol side-chain cleavage enzyme system (*CYP11A*) *(shaded)* with decreasing effectiveness. Decreased CYP11B1 activity will lead to lower levels of cortisol and increased levels of the upstream precursor 11-deoxycortisol. Decreased CYP11B2 will lead to lower aldosterone and higher 11-deoxycorticosterone levels, whereas decreased CYP11A will lead to generally decreased steroidogenesis. *3β-HSD*, 3β-hydroxysteroid-dehydrogenase; *CYP21*, 21-hydroxylase; *CYP17*, 17-hydroxylase and 17, 20-lyase

bolus of etomidate was assumed by many intensive care physicians to give only transient, clinically non-relevant hormonal changes [4–6]. This assumption was mainly based on small studies in healthy adults undergoing elective surgery and may not be applicable in children with septic shock, who are at risk for adrenal insufficiency. We have previously shown that children dying from meningococcal septic shock showed signs of inappropriate adrenal function on PICU admission, i.e. relatively low cortisol levels and extremely high adrenocorticotropic hormone (ACTH) levels, which related independently to parameters of disease severity and the use of one single bolus of etomidate for rapid sequence intubation [7]. The aim of this study was to examine the effect that etomidate exerted on adrenal function during the first 24 h after PICU admission in our cohort of children with meningococcal sepsis.

Materials and methods

Patients

The group consisted of 69 previously healthy children (42 boys and 27 girls) consecutively admitted to the PICU of the Erasmus MC–Sophia Children's Hospital, with a clinical picture of meningococcal sepsis, defined as sepsis with petechiae and/or purpura as described previously [8–10]. Blood cultures revealed *Neisseria meningitidis* in 58 children. Nine children who received corticosteroid therapy for suspected adrenal insufficiency before admission were excluded. Children who received corticosteroid therapy after admission were included until they received corticosteroids. The lack of research staff to ensure an adequate 24-h stand-by service necessitated two study periods: from October 1997 to October 1999 and from October 2001 to January 2004. The study was approved by the local medical ethics committee and adhered to the tenets of the Declaration of Helsinki.

Concomitant therapy

Concomitant therapy on admission included antibiotics (cefotaxime) and administration of fluids in all 60 children and inotropics in 51 children. On admission 31 children were mechanically ventilated, whereas 29 children were not. Mechanically ventilated children were intubated at a median of 2 h and 40 min (range 5 min to 7 h) before study enrolment with etomidate ($n = 23$) or with combinations of opiate agonists, propofol, ketamine or midazolam ($n = 8$). The median dose of the etomidate bolus was 0.29 mg/kg (range 0.20–0.67 mg/kg) and was significantly higher in children who died than in those who survived (0.46 vs 0.29, $p = 0.038$). The sedatives and doses used for rapid-sequence intubation depended on the physicians' choice. After admission four more children were intubated with etomidate. Mechanically ventilated children were all intubated for their clinical status only and were sedated with benzodiazepines and/or morphine. On admission, patients received intravenous glucose at a rate of 4–6 mg/kg/min.

Clinical parameters

Disease severity was determined using the Pediatric Risk of Mortality score (PRISM II) [11] during the first 6 h of admission. We recorded etomidate use, respiratory and inotropic support, quantified with vasopressor score of Wernovsky on admission [12].

Collection of blood samples and analysis

Arterial blood samples were obtained as soon as possible after admission and at 12 h and 24 h thereafter for determination of ACTH, 11-deoxycortisol, cortisol, glucose, lactate and interleukin (IL)-6 [8, 13].

Statistics

Results are expressed as medians unless specified otherwise. We used Mann–Whitney U, chi-square or Fisher's exact test, Spearman's correlation coefficient (r) and analysis of covariance (ANCOVA). The graph of the course of cortisol/ACTH ratios was constructed using mixed-model analysis of variance. Two-tailed p-values of < 0.05 were considered statistically significant.

Results

Clinical parameters on admission

Children who had been intubated before admission, independently of etomidate use, had significantly higher disease severity parameters – such as PRISM score, IL-6, and lactate levels – and vasopressor score than children who were not intubated, whereas none of these parameters significantly differed between children who were intubated with or without etomidate (Table 1). Arterial glucose levels were significantly lower in children who were intubated with etomidate than in children who were not intubated ($p = 0.023$) and tended to be lower than in children who were intubated without etomidate ($p = 0.082$).

Adrenal function on admission

On admission, cortisol levels were significantly lower and ACTH levels significantly higher with concomitantly lower cortisol/ACTH ratios in children who were intubated with etomidate than in those who did not receive etomidate, independently of intubation (Table 1). Furthermore, children who were intubated with etomidate had significantly higher 11-deoxycortisol levels with concomitantly lower cortisol/11-deoxycortisol ratios than children who did not receive etomidate, independently of intubation. Compared to non-stressed values, 11-deoxycortisol levels were elevated in 95% of the children who received etomidate and in 65% of the children who did not receive etomidate ($p = 0.019$), independently of intubation. Neither time from intubation to admission nor etomidate dose per kilogram body weight correlated significantly with serum levels of cortisol, ACTH, 11-deoxycortisol or their ratios on admission (data not shown).

ANCOVA revealed ACTH levels to be significantly related to intubation with etomidate and disease severity, as shown by lactate levels ($R^2 = 0.54$), whereas age and

Table 1 Patients' characteristics and adrenal function on admission according to intubation and etomidate use

	Reference values	Intubated with etomidate ($n = 23$)	Intubated without etomidate ($n = 8$)	Not intubated ($n = 29$)
Age (years)		3.7 (0.9–9.4)	4.0 (0.8–7.6)	4.9 (2.3–10.4)
Sex (M/F)		19/4 [a, b]	2/6	16/13
Septic shock (%)		23 (100) [b]	8 (100)	20 (69)
Vasopressor score		40 (15–60) [b]	35 (6–105) [b]	5 (0–18) [a, c]
PRISM score		25 (20–33) [b]	26 (18–35) [b]	17 (9–20) [c]
Survival (%)		16 (70) [b]	7 (88)	29 (100) [c]
IL-6 x 10^3 (pg/ml)	< 0.01	135.0 (40.0–853.1) [b]	63.2 (15.1–70.5)	8.3 (1.1–80.9) [c]
Lactate (mmol/l)	< 2.0	4.7 (3.1–6.9) [b]	4.0 (2.6–6.8)	3.0 (2.2–4.6) [c]
Glucose (mmol/l)	2.6–11.0	5.7 (4.1–7.7) [b]	7.8 (5.5–14.2)	7.7 (6.7–8.7) [c]
Cortisol (nmol/l)	200–800 *	620 (502–782) [a, b]	1173 (818–1263)	1089 (971–1346)
ACTH (pmol/l)	< 11 *	146.1 (79.3–222.0) [a, b]	53.7 (10.8–116.0)	14.0 (5.6–64.2)
Cortisol/ACTH (nM/pM)		4.7 (2.3–8.4) [a, b]	20.7 (3.5–112.7)	89.4 (21.0–205.2)
11-deoxycortisol (nmol/l)	< 50 *	181 (137–248) [a, b]	49 (36–69)	62 (44–88)
Cortisol/11-deoxycortisol		3.2 (2.1–4.3) [a, b]	21.6 (16.7–25.8)	19.2 (13.6–24.5)

All values are expressed as median (25th to 75th percentiles); * Non-stressed reference values (for cortisol morning values at 8:00 AM); [a] Significantly different from children who were intubated without etomidate, $p < 0.05$; [b] Significantly different from patients who were not intubated, $p < 0.05$; [c] Significantly different from patients who were intubated, independently of etomidate use, $p < 0.05$

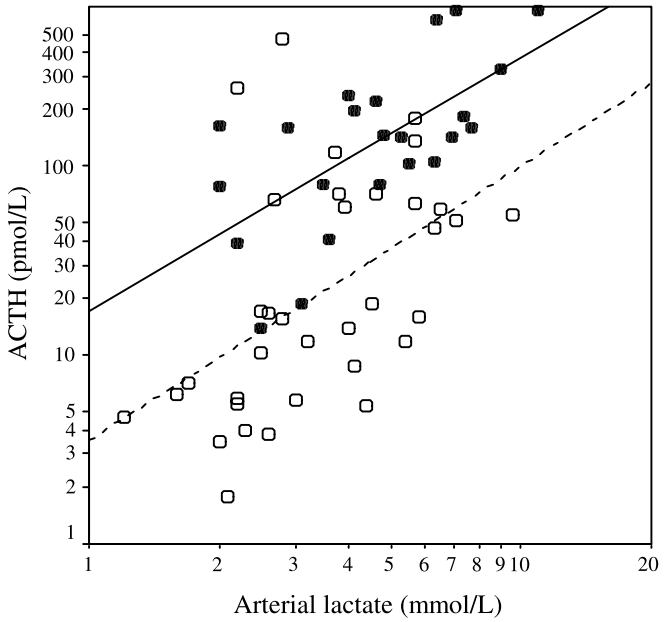

Fig. 2 Relation between ACTH and arterial lactate levels, depending on etomidate use. After adjustment for arterial lactate levels, using ANCOVA, mean ACTH levels were 4.1 times higher in etomidate use ($p < 0.001$). Children who received etomidate (●, *continuous line*) and children who did not receive etomidate (○, *dotted line*). Data of children intubated without etomidate or those not intubated were pooled, as they did not significantly differ

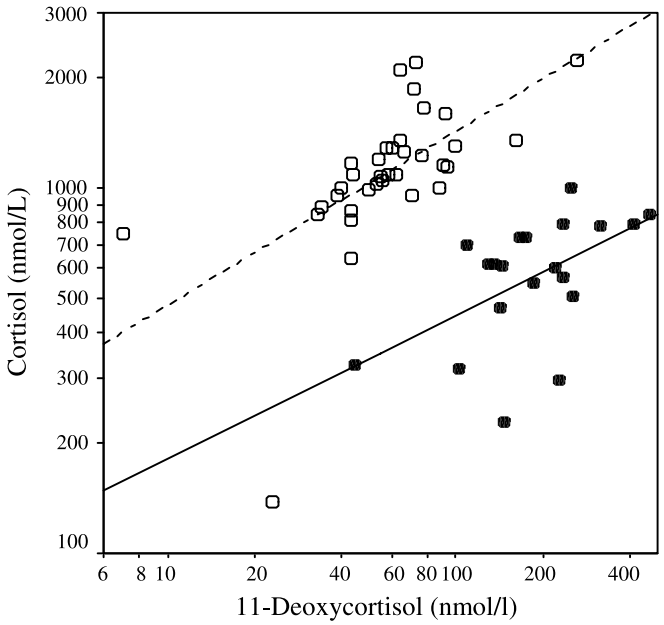

Fig. 3 Relation between cortisol and 11-deoxycortisol levels, depending on etomidate use. After adjustment for 11-deoxycortisol levels, using ANCOVA, mean cortisol levels were 3.2 times lower in case of etomidate use ($p < 0.001$). Children who received etomidate (●, *continuous line*) and children who did not receive etomidate (○, *dotted line*). Data of children intubated without etomidate or those not intubated were pooled, as they did not significantly differ

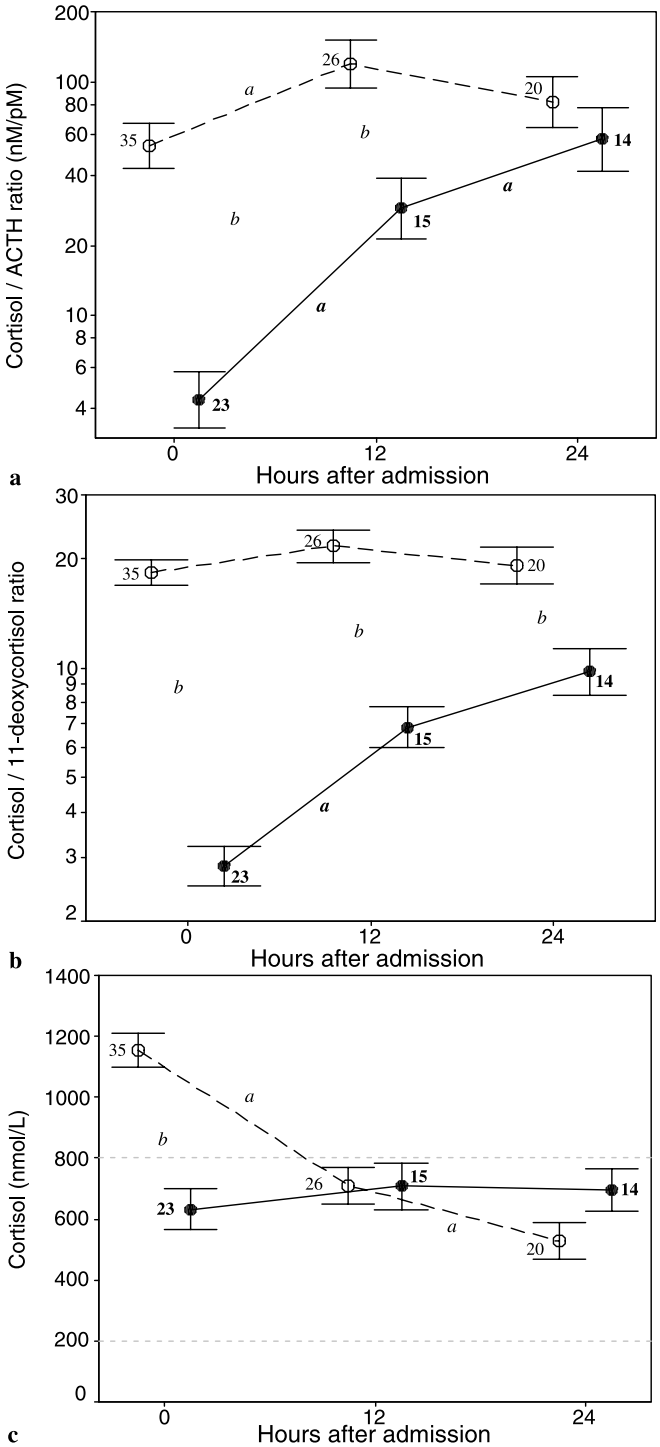

Fig. 4 Cortisol/ACTH ratios (**a**), cortisol/11-deoxycortisol ratios (**b**) and cortisol levels (**c**) according to patients' actual etomidate use during the first 24 h after admission. The three profiles differed between the groups along time ($p < 0.001$). Data shown are geometric means with standard errors. Children who received etomidate (●, *continuous line*) and children who did not receive etomidate (○, *dotted line*). Within-group difference between successive time point (*a*, $p < 0.05$). Between-group difference at time points (*b*, $p < 0.05$). *Numbers* alongside data-points indicate numbers of children

gender were not. When children were intubated with etomidate, ACTH levels were 4.1 times higher for comparable lactate levels (Fig. 2). In contrast, we found no difference in the relation of ACTH with lactate between children who were intubated without etomidate and those who were not intubated (ANCOVA, $p = 0.222$). A similar pattern was found for ACTH levels with IL-6 levels and etomidate ($R^2 = 0.55$), in which ACTH levels were 3.3 times higher if children were intubated with etomidate. ANCOVA revealed 11-deoxycortisol levels and intubation with etomidate to be significantly related to cortisol levels ($R^2 = 0.57$), whereas age and gender were not. Cortisol levels were 3.2 times lower, for comparable 11-deoxycortisol levels, if children were intubated with etomidate (Fig. 3). In contrast, we found no difference in the relation of cortisol with 11-deoxycortisol, between children who were intubated without etomidate and those who were not intubated (ANCOVA, $p = 0.303$).

Adrenal function time course

Within 5 h after study enrolment four further children were intubated with etomidate. Seven children received glucocorticoid treatment for suspected adrenal insufficiency after study enrolment; six of them (intubated with etomidate) within 5 h and one (intubated without etomidate) after 55 h. Eight children died due to hemodynamic failure at median 11 h after PICU admission (range 8–43 h), seven of whom had received etomidate. Within 24 h both cortisol/ACTH and cortisol/11-dexoycortisol ratios increased significantly in children who had received etomidate, but not in children who did not receive etomidate, resulting in comparable cortisol/ACTH ratios with still decreased cortisol/11-deoxycortisol ratios 24 h after admission (Fig. 4).

Discussion

This retrospective study shows major differences in ACTH, cortisol and 11-deoxycortisol levels between children intubated with one single bolus of etomidate and those who did not receive etomidate, independently of intubation.

Although our study was not designed to investigate the direct relation between etomidate administration and adrenal function, we found significantly more signs of impaired adrenal function, as shown by the combination of significantly lower cortisol with increased ACTH levels, in children who received etomidate than in those who did not, even after correction for disease severity (Fig. 2). On admission cortisol levels were 3.2 times lower and ACTH levels were 4.1 times higher in children who received etomidate than in those who did not. Serum 11-deoxycortisol (the precursor of cortisol that exerts no endocrine actions) was significantly higher, and cortisol/11-deoxycortisol lower, in children who received etomidate than in those who did not, indicating impaired 11β-hydroxylase activity (CYP11B1, Fig. 1). This is in accordance with in vitro and in vivo studies that show etomidate to interfere mainly with 11β-hydroxylase, and at higher concentrations also with 11β- and 18-hydroxylase (CYP11B2) and the cholesterol side-chain cleavage enzyme system (CYP11A) [2, 14, 15–17]. Despite the fact that etomidate is known to suppress adrenal function in a dose-dependent manner in vitro [14], we did not find such a relation, probably due to lack of study power. However, the dose of etomidate was higher in children who died than in those who survived. Because we studied the effect of etomidate retrospectively in an uncontrolled setting, it is difficult to report on relevant clinical deterioration, such as persistent hypotension or the course of glucose levels. We found, nevertheless, significantly lower glucose levels on admission in children receiving etomidate than in those who did not. Furthermore, in this study seven of the eight children who died during admission received etomidate. Significant but transient adrenocortical suppression 24 h after a single bolus of etomidate has been described [18, 19]. Although we found cortisol concentrations and cortisol/ACTH ratios to reach comparable levels between the studied groups more than 24 h after intubation, cortisol/11-deoxycortisol ratios were still significantly decreased in children who received etomidate compared to those who did not, indicating adrenocortical suppression at the level of 11β-hydroxylase. Future investigations using corticotropin test should be performed to study the duration of this adrenocortical suppression.

In summary, our data imply that even one single bolus of etomidate negatively influences adrenal function for at least 24 h and therefore might increase risk of death. As recently stated [6], considerable caution should accompany the administration of etomidate in patients with septic shock.

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