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ORIGINAL

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Duration of adrenal inhibition following a single dose of etomidate in critically ill patients

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Abstract *Objective:* To determine the incidence and duration of adrenal inhibition induced by a single dose of etomidate in critically ill patients. *Design:* Prospective, observational cohort study. *Setting:* Three intensive care units in a university hospital. *Patients:* Forty critically ill patients without sepsis who received a single dose of etomidate for facilitating endotracheal intubation. *Measurements and main results:* Serial serum cortisol and 11β-deoxycortisol samples were taken at baseline and 60 min after corticotropin stimulation test (250 μg 1–24 ACTH) at 12, 24, 48, and 72 h after etomidate administration. Etomidate-related adrenal inhibition was defined by the combination of a rise in cortisol less than 250 nmol/l (9 μg/dl) after ACTH stimulation and an excessive accumulation of serum 11β-deoxycortisol concentrations at baseline. At 12 h after etomidate administration, 32/40 (80%) patients fulfilled the diagnosis criteria for etomidate-related adrenal insufficiency. This incidence was significantly lower at 48 h (9%) and 72 h (7%). The cortisol to 11β-deoxycortisol ratio (F/S ratio), reflecting the intensity of the 11β-hydroxylase enzyme blockade, improved significantly over time. *Conclusions:* A single bolus infusion of etomidate resulted in wide adrenal inhibition in critically ill patients. However, this alteration was reversible by 48 h following the drug administration. The empirical use of steroid supplementation for 48 h following a single dose of etomidate in ICU patients without septic shock should thus be considered. Concomitant serum cortisol and 11β-deoxycortisol dosages are needed to provide evidence for adrenal insufficiency induced by etomidate in critically ill patients.

Keywords Etomidate · Adrenal · Corticotropin · Critical care

Introduction

Etomidate is a first-line anaesthetic agent for the facilitation of endotracheal intubation in haemodynamically unstable patients because of its excellent haemodynamic tolerance [1–4]. However, the safety of etomidate as an anaesthetic induction agent for critically ill patients is in debate, since its administration inhibits the 11β-hydroxylase enzyme that converts 11β-deoxycortisol into cortisol in the adrenal gland. Continuous infusion

of etomidate has been withdrawn because it was found to increase patient mortality incurred from long-term adrenal suppression [5]. A single dose of etomidate can also blunt the adrenal function for 4–24 h [6–8], and was among factors associated with relative adrenal deficiency in critically ill patients [9]. Relative adrenal deficiency means a lack of adrenocortical reserve as determined by an inadequate response to synthetic corticotropin stimulation, and has also been found in critical illness, e.g. traumatic brain injury, septic shock, and haemorrhagic shock [10, 11–14]. Therefore, a single dose of etomidate in those clinical settings raised legitimate concerns as it may worsen patient outcome [15–19].

In the clinical dilemma regarding the management of endotracheal intubation in haemodynamically unstable patients, two approaches have been proposed: elimination of the use of etomidate or systematic concomitant administration of corticosteroids [16, 20]. However, little is known about the duration of the drug-induced adrenal inhibition, which ideally requires serial measurements of serum cortisol and concomitant 11β-deoxycortisol to explore the drug's effects on adrenal function. We therefore conducted a prospective, observational study in critically ill patients without septic shock, who had received, in the field or in the emergency department, a single injected dose of etomidate to facilitate endotracheal intubation. The purpose of this study was to determine the incidence and the duration of the etomidate-induced adrenal inhibition by means of serial serum cortisol and 11β-deoxycortisol dosages at baseline and after corticotropin stimulation test during a 72-h follow-up study.

Methods

Study population

This prospective, observational study was conducted from October 2005 to January 2006. The local ethics committee approved the design of the study, and written informed consent about this study was obtained from the patients or their relatives.

Adult patients were eligible if they had required endotracheal intubation for vital distress in the field or in the emergency department, using a rapid-sequence induction with intravenous injection of etomidate and suxamethonium. The induction time was considered as the reference time (H0). If necessary, sedation was maintained using continuous intravenous infusion of sedative/analgesic agents (midazolam, propofol, sufentanil, remifentanil). Patients were excluded from the study if they were admitted to the intensive care unit (ICU) more than 12 h after induction time, had septic shock, and/or exhibited other confounding factors for adrenal exploration. Data were collected on admission and at 12, 24, 48 and 72 h following the administration of etomidate while the patient stayed in the ICU.

Further details are provided in the ESM.

Hormonal assays

The adrenal function was assessed using the high-dose corticotropin stimulation test (CST). Serum total cortisol and concomitant 11β-deoxycortisol concentrations were determined at baseline (T0) and 60 min after intravenous administration of 250 μg of synthetic 1–24 ACTH (Synacthen®, Novartis Pharma, Rueil-Malmaison, France) (T60). This exploration was performed at 12, 24, 48 and 72 h following the administration of etomidate (H12, H24, H48, H72).

Further details are provided in the ESM.

Diagnosis of etomidate-induced adrenal insufficiency

A lack of cortisol response to 1–24 ACTH stimulation with a concomitant accumulation of 11β-deoxycortisol in serum was used as a diagnosis criteria to establish etomidate-related adrenal insufficiency. Specifically, an increase in serum cortisol concentration of less than 250 nmol/l (9 μg/dl) irrespective of basal cortisol level was used as the diagnostic criterion for CST nonresponders (delta cortisol) [10, 21]. Because reference values of 11β-deoxycortisol for ICU patients are rare [22], we investigated a pilot group of 10 critically ill patients who were given midazolam or propofol for facilitating endotracheal intubation. All these patients gave informed consent, had similar inclusion criteria as the study group, and were CST responders as assessed 12 h after the hypnotic drug administration. On the basis of their results, CST nonresponders who also had an accumulation of 11β-deoxycortisol in serum of more than 8 nmol/l (0.29 μg/dl) at baseline were considered as having etomidate-related adrenal insufficiency. In addition, the serum cortisol to 11β-deoxycortisol ratio (F/S ratio) was determined. This parameter indirectly reflects the 11β-hydroxylase enzyme activity.

Further details are provided in the ESM.

Statistical analysis

Descriptive statistics included frequencies and percentages for categorical variables, and medians and range for continuous-level variables, unless otherwise stated. Analysis for statistical significance of temporal changes during the study period was performed using the random effect linear model. Bonferroni's correction was applied for multiple comparisons where appropriate. Nonparametric Wilcoxon and Mann–Whitney tests were used for intragroup and intergroup analysis, respectively. The relation

between hormonal changes and patient outcome (length of ICU stay, duration of mechanical ventilation) or etomidate dosage was tested using simple linear square regression. Statistical significance was established at $p < 0.05$. All statistical analyses were performed using Stat version 8.0 software (Stata Corp., College Station, TX).

Results

Of the 46 patients eligible during the study period, 6 were excluded (1 because of death before H12, 1 for repeated doses of etomidate, 2 for CST for another reason than the study protocol, 2 for concomitant treatment with steroids). The demographic characteristics of the 40 included patients are shown in Table 1. Of the 18 trauma patients (Injury Severity Score 20, range 9–34), there were 8 with severe traumatic brain injury (Glasgow Coma Scale score less than 9). Etomidate (median dosage 0.33 mg/kg, range 0.22–0.80) was administered on field in 22 patients with a median delay of 1.5 h (0.5–7.0) between administration of the drug and their admission to the emergency department. The number of patients explored for adrenal function was 40 at H12, 39 at H24, 32 at H48, and 27 at H72 because of the discharge of some patients from the ICU.

Individual data of serum cortisol and 11β-deoxycortisol concentrations at baseline and after 1–24 ACTH administration during the study period are shown in Fig. 1. The baseline serum 11β-deoxycortisol concentrations of the population largely exceeded those found in the pilot group of 10 ICU patients without etomidate (Fig. 1a).

Table 1 Demographic and clinical characteristics of the 40 ICU patients on admission to the emergency room

Age, years	44 (19–84)
Males/females	26/14
SAPS II	35 (12–70)
SOFA score	5 (1–15)
Glasgow Coma Scale score	13 (3–15)
Reasons for endotracheal intubation	
Trauma	18
Subarachnoid haemorrhage	8
Acute poisoning	4
Stroke	3
Cardiovascular collapse	5
Status epilepticus	1
Acute respiratory distress	1
MABP, mmHg	90 (48–165)
HR, beats/min	90 (50–130)
Vasoactive agents on admission	12
Death in ICU	3
Length of mechanical ventilation, days	4 (1–80)
Length of ICU stay, days	8 (2–100)

Values are median (range) or *n*; *SAPS*, Simplified Acute Physiology Score; *SOFA*, Sequential Organ Failure Assessment; *MABP*, mean arterial blood pressure; *HR*, heart rate

This accumulation of serum 11β-deoxycortisol declined over time. Concomitantly, most patients had a pronounced blunted cortisol response to the 1–24 ACTH stimulation at H12, which was also reversible over time (Fig. 1b). Thirty-two of 40 patients (80%) fulfilled the diagnostic criteria for etomidate-related adrenal insufficiency at H12, i.e. a cortisol response of less than 250 nmol/l (9 μg/dl) and an accumulation of baseline serum 11β-deoxycortisol concentrations of more than 8 nmol/l (0.29 μg/dl) (Table 2). This proportion was significantly lower at H48 (9%) and H72 (7%), as both numbers of CST nonresponders and of patients with accumulated serum 11β-deoxycortisol decreased accordingly (Table 2). The intensity of the etomidate-induced 11β-hydroxylase enzyme blockade

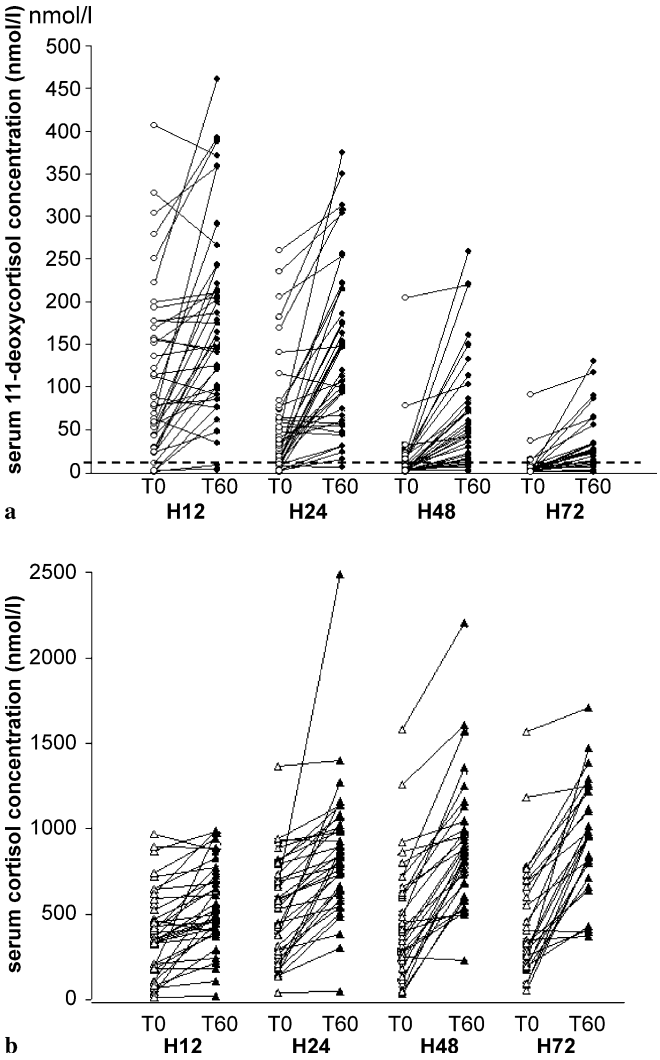

Fig. 1 Individual serum concentrations of **a** 11β-deoxycortisol and **b** cortisol at baseline (*T*0) and 60 min after 1–24 ACTH administration (*T*60) at H12, H24, H48 and H72 following a single dose of etomidate. The reference value for serum 11β-deoxycortisol at baseline (8 nmol/l) is plotted (*dotted line*)

Table 2 Time course of biochemical data over the study period. Serum cortisol and 11β-deoxycortisol concentrations (nmol/l) were determined at baseline (T0) and 60 min after 1–24 ACTH administration (corticotropin stimulation test, CST; T60) to determine cortisol and 11β-deoxycortisol responses (delta cortisol, delta 11β-deoxycortisol). Patients with an etomidate-related adrenal insufficiency (AI) were defined as having accumulation of 11β-deoxycortisol in serum of more than 8 nmol/l (0.29 μg/dl) at baseline and a cortisol response (delta cortisol) of less than 250 nmol/l (9 μg/dl) (CST nonresponders)

	H 12 ($n=40$)	H 24 ($n=39$)	H 48 ($n=32$)	H 72 ($n=27$)
Cortisol, nmol/l				
T0	372 (11:969)	561 (40:1365)	418 (35:1577)	352 (56:1568)
Delta cortisol	133 (–95:785)	253 (–8:1818) *	530 (–19:869)	456 (–8:1251)
Delta cortisol < 250 nmol/l	33 (82)	19 (49) *	7 (22)	6 (22)
11β-Deoxycortisol, nmol/l				
T0	84 (2:407)	35 (2:261) *	5 (1:204) **	3 (1:91)
Delta 11β-deoxycortisol	48 (–63:291)	66 (–17:325)	43 (–1:236)	24 (0:127) ***
11β-Deoxycortisol > 8 nmol/l	36 (90)	33 (85)	12 (38) **	5 (19)
Etomidate-related AI	32 (80)	18 (46) *	3 (9) **	2 (7)
F/S ratio				
T0	4 (1:72)	11 (2:158) *	66 (4:219) **	105 (13:291) ***
T60	3 (1:73)	6 (2:54)*,^	21 (4:98) **,^	36 (7:237) ***,^
Serum protein, g/l	54 (33:71)	56 (33:76)	58 (38:78)	57 (43:71)

Values are median (range) or *n* (%); F/S ratio, serum cortisol to 11β-deoxycortisol ratio; * $p<0.05$ H24 vs. H12: ** $p<0.05$ H48 vs. H24; *** $p<0.05$ H72 vs. H48; ^ $p<0.05$ T60 vs. T0 (F/S ratio)

progressively declined, as reflected by significant changes in F/S ratio over time (Table 2, Fig. 2). At H24, H48 and H72, baseline F/S ratios were significantly higher than after 1–24 ACTH test ($p < 0.05$). No changes in basal serum cortisol or in serum total protein were found during the study period.

Patients had no significant changes in their SOFA score, MABP and heart rate during the study period (data not shown). The incidence of patients requiring norepinephrine support remained unchanged during the study period: 60% of the population at H12, 49% at H24, 56% at H48, and 52% at H72. However, the dose of norepinephrine at H24 was significantly larger in patients with etomidate-related adrenal inhibition ($n = 9/18$) than in those without adrenal inhibition ($n = 10/21$) – 1.8 mg/h (0.2–11.0) vs 0.2 mg/h (0.1–1.6), respectively ($p < 0.01$) – despite comparable MABP between these two subgroups of patients – 82 mmHg (54–105) vs 90 mmHg (73–125), respectively. Dobutamine was required for 28% of the population at H12, with a median infusion dose of 20 mg/h at H12 and with no difference regarding the presence or the absence of etomidate-induced adrenal inhibition. No significant relationship was found between hormonal changes (delta cortisol, baseline 11β-deoxycortisol, F/S ratio) measured at H12 and etomidate dosage or patient outcome (length of ICU stay, duration of mechanical ventilation).

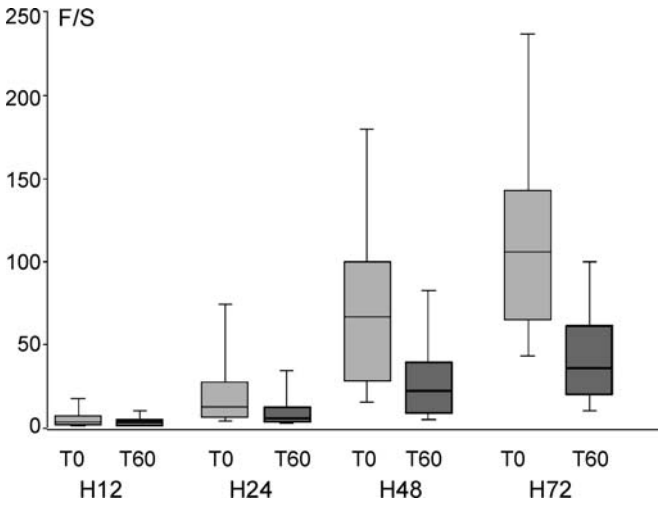

Fig. 2 Time course of serum cortisol to 11β-deoxycortisol ratio (*F/S*) at baseline (*T*0) and 60 min after 1–24 ACTH administration (*T*60) at H12, H24, H48 and H72 following a single dose of etomidate. *Box-plots* indicate 25th and 75th percentiles with the median, and *whiskers* the 95% confidence interval

Discussion

A single dose of etomidate resulted in an adrenal inhibition through its specific 11β-hydroxylase enzyme blockade in most of our group of ICU patients without septic shock (80%). However, this alteration was reversible, as a dramatic reduction in the incidence of patients with impaired adrenal function occurred within 48 h following the drug administration.

Because etomidate blocks the conversion of 11β-deoxycortisol to cortisol, cortisol synthesis and secretion fall while 11β-deoxycortisol accumulates in serum. We thus used two diagnostic criteria to define etomidate-induced adrenal inhibition: a cortisol increment

of less than 250 nmol/l (9 μg/dl) after CST, and a serum level of 11β-deoxycortisol exceeding 8 nmol/l (0.29 μg/dl) at baseline. Although the most appropriate definition of what constitutes adrenal insufficiency in ICU is still in debate, changes in serum total cortisol measured 60 min after stimulation with 250 μg corticotropin are probably the best predictor of the maximal secreting capacity of the adrenal glands in septic and in non-septic patients [12, 21, 22]. A delta cortisol value of less than 250 nmol/l (9 μg/dl) had a specificity of 96%, a positive predictive value of 94%, and a positive likelihood ratio of over 10 [22]. Serum total cortisol was assayed in this study because serum free cortisol measurements were not available. However, exogenous ACTH administration has no effect on albumin or cortisol-binding globulin levels; thus, the increment in total cortisol should not be influenced by serum albumin levels [23]. The time interval of 12 h left between the ACTH tests did not affect the subsequent exploration of adrenocortical reserve because there was no evidence of exhaustion in the delta cortisol amplitude during the study period. In addition, serum cortisol levels were found to return to baseline values around 6 h after a 250-μg dose of ACTH [24].

References values for serum 11β-deoxycortisol after a single dose of thiopentone in unstressed surgical patients ranged between 0.2 and 1.5 nmol/l (0.007–0.054 μg/dl) [6]. In 44 critically ill patients without sepsis, the median value of serum 11β-deoxycortisol was 2.6 nmol/l (interquartile range 1.4–6.9) (0.095 μg/dl, interquartile range 0.051–0.250) [22]. In line with that study, we took the highest value of baseline serum 11β-deoxycortisol (8 nmol/l or 0.29 μg/dl) obtained 12 h after administration of midazolam or propofol to facilitate tracheal intubation in a pilot group of 10 CST responders. Our choice reflected the best compromise to detect relevant abnormalities in serum 11β-deoxycortisol concentrations. This was indirectly reflected by the fact that the proportion of patients with abnormal serum 11β-deoxycortisol concentrations was close to that of CST nonresponders at H12 (90% and 82%, respectively).

We found a high incidence of patients exhibiting etomidate-induced adrenal inhibition at H12 (80%). Etomidate has repeatedly been identified as one contributing factor to relative adrenal insufficiency in septic patients [9, 19, 25, 26]. Because relative adrenal insufficiency has also been reported in septic patients without the use of etomidate [10, 22, 23], the interpretation of those hormonal abnormalities could be speculative in the absence of concomitant serum 11β-deoxycortisol measurements. This might also explain why conflicting data have been reported regarding the relationship between the use of etomidate and outcome in patients with septic shock [19, 27]. Because assessment of adrenal function is particularly difficult in critically ill patients, our study underscores the interest of concomitant dosages of serum cortisol and 11β-deoxycortisol to provide evidence for adrenal insufficiency specifically induced by etomidate. There are no other clinical situations resulting in adrenal inhibition with a concomitant accumulation of serum 11β-deoxycortisol, apart from the rare inherited deficiency of 11β-hydroxylase.

The vast majority of our patients did not meet the diagnosis criteria of etomidate-induced adrenal inhibition at H48, and no further hormonal changes were noted at H72. This duration of adrenal inhibition was somewhat longer than the 12 h found in patients undergoing tracheal intubation in the emergency room, probably because the criterion for defining CST nonresponders was too restrictive in that study [8]. In addition, the correction of serum accumulation of 11β-deoxycortisol concentrations was slower than that of cortisol derangement (see Table 2). In our population, four patients had baseline cortisol level of less than 82.8 nmol/l (3 μg/dl) at H12, a cut-off value indicating a definite adrenal insufficiency in septic patients [19]. These four patients had no evidence of etomidate-related adrenal inhibition by H48, suggesting that baseline cortisol level alone is not predictive of the potential recovery of adrenal function following etomidate. Conversely, the temporal course of this adrenal function recovery was best depicted by the changes in F/S ratio over time (see Fig. 2). This ratio is lowered in the case of blockade of 11β-hydroxylase, as expected. It was used as a marker for etomidate-induced adrenal insufficiency in children with meningococcal sepsis [25]. While F/S ratio was comparable between baseline and after ACTH stimulation in our pilot group of 10 patients, we found higher F/S ratios at baseline than after ACTH stimulation in the study population, even at H72. This indicates a prolonged limited capacity of 11β-hydroxylase to convert 11β-deoxycortisol into cortisol when the adrenal gland is stimulated.

From our findings, systematic steroid supplementation for the first 48 h should be considered whenever etomidate is administered to facilitate tracheal intubation in haemodynamically unstable patients without septic shock. The fact that our patients with etomidate-induced adrenal inhibition received larger doses of norepinephrine at H24 to maintain MABP could argue for such short-term substitution. The choice of induction agent for those patients is complex, and the use of alternatives to etomidate, i.e. midazolam, propofol, and thiopental, can expose those patients to unpredictable cardiovascular reactions [2]. It should be kept in mind that haemodynamic instability can affect mortality during the induction phase of anaesthesia and is a key factor associated with increased mortality after severe traumatic brain injury [28, 29]. In the absence of prospective studies exploring the potential benefits of steroid supplementation with the use of etomidate, no clinical recommendation can be formulated. However, the incidence and duration of etomidate-related adrenal inhibition cannot be ignored any

longer, and our findings may help physicians to appreciate the benefit–risk ratio when using etomidate in critically ill patients.

In conclusion, a single dose of etomidate resulted in marked adrenal inhibition in critically ill patients without sepsis. This adrenal inhibition was reversible as the hormonal derangement was largely corrected by 48 h.

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