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The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock

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Abstract *Rationale:* Use of etomidate in the critically ill is controversial due to its links with an inadequate response to corticotropin and potential for excess mortality. In a septic shock population, we tested the hypotheses that etomidate administration induces more non-responders to corticotropin and increases mortality and that hydrocortisone treatment decreases mortality in patients receiving etomidate. *Methods:* An a-priori sub-study of the CORTICUS multi-centre, randomised, double-blind, placebo-controlled trial of hydrocortisone in septic shock. Use and timing of etomidate administration were collected. Endpoints were corticotropin response and all-cause 28-day mortality in patients receiving etomidate.

Measurements and main results: Five hundred patients were recruited, of whom 499 were analysable; 96 (19.2%) were administered etomidate within the 72 h prior to inclusion. The proportion of non-responders to corticotropin was significantly higher in patients who were given etomidate in the 72 h before trial inclusion than in other patients (61.0 vs. 44.6%, $P = 0.004$). Etomidate therapy was associated with a higher 28-day mortality in univariate analysis ($P = 0.02$) and after correction for severity of illness (42.7 vs. 30.5%; $P = 0.06$ and $P = 0.03$) in our two multi-variant models. Hydrocortisone administration did not change the mortality of patients receiving etomidate (45 vs. 40%).

Conclusions: The use of bolus dose etomidate in the 72 h before study inclusion is associated with an increased incidence of inadequate response to corticotropin, but is also likely to be associated with an increase in mortality. We recommend clinicians demonstrate extreme caution in the use of etomidate in critically ill patients with septic shock.

Keywords Etomidate · Relative adrenal insufficiency · Septic shock · Mortality · Hydrocortisone

Introduction

Septic shock is a major cause of morbidity and mortality worldwide [1–4]. The administration of moderate doses of corticosteroids for sepsis in septic shock has been controversial for many years [5–7]. Recent meta-analyses, reviews and guidelines have advocated the use of ‘low-dose’ hydrocortisone in septic shock [8–13]. It is clear that an altered response to the ACTH stimulation test is associated with an increased mortality in patients with septic shock [14–18].

Many critically ill patients require mechanical ventilation, and the imidazole anaesthetic agent etomidate is often used to facilitate endotracheal intubation in these patients. It has been known for many years that etomidate inhibits adrenocortical steroid synthesis by reversibly blocking the action of the enzyme 11- β -hydroxylase [19, 20]. This can last for at least 24 h following a single bolus of etomidate [20–22]. The deleterious effects of etomidate by infusion were first recognised in the critically ill when an excess mortality was identified in trauma patients who received infusions of etomidate for sedation [23, 24]. Its use is now recognised as an important cause of inadequate response to corticotropin (IRC) in the critically ill [18, 25]. Some authorities have even recommended that etomidate administration either be discontinued altogether or should always be accompanied by steroid replacement therapy to counter these effects [26–29]. The evidence for a direct effect of a single bolus dose of etomidate on mortality in these patients is more controversial, with some studies showing an increased mortality [14, 30–32] and others showing no difference [33, 34]. Many of these studies were small and underpowered. Despite this evidence many clinicians still use etomidate in the critically ill because of its remarkably safe cardiovascular profile [33, 34].

Using data from CORTICUS, a large, prospective multi-centre study of hydrocortisone treatment in septic shock, we tested the hypotheses that bolus doses of etomidate results in an increased proportion of non-responders to corticotropin and an increase in mortality, and that hydrocortisone treatment decreases mortality in patients receiving etomidate.

Methods

Patients

This study is an a-priori sub-study of the CORTICUS study, which was a multi-centre, randomised, double-blind, placebo-controlled trial of low-dose hydrocortisone in septic shock [35]. Following formal approval by the Ethics Committees of the 52 participating adult intensive care units (ICUs), adult patients were enrolled from

March 2002 until November 2005. Patients in participating ICUs were included if they met the inclusion criteria, including: (1) clinical evidence of infection, (2) evidence of a systemic response to infection, (3) continued evidence of shock within the previous 72 h defined by a systolic blood pressure (SBP) <90 mmHg despite adequate fluid replacement OR need for vasopressors for at least 1 h, and evidence of hypoperfusion or organ dysfunction attributable to sepsis and (4) informed consent according to local regulations [35]. Notable exclusion criteria included underlying disease with a poor prognosis, immunosuppression and prior administration of corticosteroids [35]. The use of etomidate was discouraged because of its perceived potential for adrenal suppressive effects but did not constitute an exclusion criterion. Patients received hydrocortisone hemisuccinate or placebo for 11 days in a tapering dose and then stopped [35]. Evidence-based guidelines for patient management were encouraged [36].

Data collection

Data collected included general demographics, SAPS II score [37] and the use and timing of etomidate administration over the trial period. Organ system failure was defined for each of the six major organ systems as a sequential organ failure assessment (SOFA) score of 3 or 4 points [38]. A short corticotropin test was performed using blood samples taken immediately before and 60 min after an intravenous bolus of 0.25 mg tetracosactrin (Novartis, Nuremberg, Germany, or Alliance, Chippenham, UK). Non-responders to the corticotropin test were defined by a cortisol increase of ≤ 9 $\mu\text{g/dl}$ (248 nmol l^{-1}) [39, 40]. Final analyses were undertaken in a central laboratory using the ELECSYS Cortisol assay[®] (Roche Diagnostics, Mannheim/Penzberg, Germany). Reversal of shock was defined as the maintenance of a SBP ≥ 90 mmHg without vasopressor support for ≥ 24 h. Patients were followed up for vital status at a 28-day period after randomisation. Random quality assurance evaluations were performed in 10% of all data.

Outcomes

A-priori endpoints for this sub-study were corticotropin response in patients who received etomidate, all-cause 28-day mortality in septic shock patients who received or did not receive etomidate and whether hydrocortisone decreased mortality in patients receiving etomidate. Etomidate administration was defined as any dose administered within the 72 h prior to trial randomisation (day 0). Patients receiving etomidate within 72 h of trial inclusion were prospectively defined as the patients most likely to develop IRC after etomidate administration [35].

Patients who received etomidate >72 h prior to trial inclusion were not included in the etomidate group as it was assumed that the effects of etomidate would not persist beyond 3 days.

Statistical analysis

Twenty-eight-day all-cause mortality was analysed by the Fisher's exact test for differences between treatment groups. The Fisher exact test was used when comparing responsiveness versus non-responsiveness in patients receiving etomidate or not. Multivariate analyses of the 28-day mortality were carried out using logistic regression models. Cumulative incidence of shock reversal was estimated by nonparametric methods, accounting death prior to reversal as a competing risk for the outcome. Curves were compared across groups using the Gray test. Two-sided *P*-values of 5% were considered statistically significant. Statistical analyses were performed using SAS 9.1 (SAS Inc., Cary, NC) and R 2.6.1 (<http://www.R-project.org>) software packages.

Role of the funding source

The EU Commission and other sponsors had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; or in the preparation, review or approval of the manuscript.

Results

Relevant baseline demographics of the 499 patients and in the 96 patients who received etomidate within 72 h of trial inclusion are shown in Table 1. Data on reasons for etomidate use were not collected. Etomidate was used in 96 (19.2%) patients in the 72 h before trial inclusion and a further 33 (7%) of patients in the week before, or month after, trial inclusion (total receiving etomidate at any time 129 (26%). The number of non-responders to corticotropin was significantly higher in patients who were given etomidate than in other patients [58 of 95 (61.0%), vs. 175 of 392 (44.6%), *P* = 0.004]. For patients who received etomidate within 72 h of trial inclusion, the median time between etomidate dosage and inclusion was 14.5 h [interquartile range (IQR) 4.25–28.4]. In seven patients receiving etomidate 3–7 days prior to randomisation, 3 (42.9%) were nonresponders versus 4 (57.1%) responders to corticotropin.

In a univariate analysis an increased mortality was observed in those who received etomidate (OR = 1.70, 95% CI: 1.07–2.68; *P* = 0.02) (Tables 1, 2; Fig. 1), with similar causes of death in both groups (*P* = 0.26) (Table 1). We developed two logistic regression models

adjusting for the treatment group (steroid/placebo), response to corticotropin (responder/non-responder), baseline cortisol value (as continuous variable) and SAPS II score in the first and these co-variants plus SOFA score in the second. In the first model we demonstrated a non-significant increase in mortality (OR = 1.60, 95%CI: 0.98–2.62; *P* = 0.06), and in the second model this became statistically significant (OR = 1.75, 95%CI: 1.06–2.90; *P* = 0.03) (Table 3). Hydrocortisone administration did not change the mortality of patients receiving etomidate (45 vs. 40%) (Tables 2, 3). In the hydrocortisone group and the placebo group, the cumulative incidence of shock reversal was not effected by the administration of etomidate (*P* = 0.42 and *P* = 0.41, respectively; Fig. 1). In the placebo group, mean time to reversal of shock was 6.2 days (95% CI 4.4–8.2) in those receiving etomidate and 5.7 days (95% CI 4.6–6.8) in those who did not (*P* = 0.41 by the Gray test); in the hydrocortisone group, mean time to reversal of shock was 3.0 days (95% CI: 2.5–3.5) in those receiving etomidate and 3.8 days (95% CI: 3.1–4.4) in those who did not (*P* = 0.42 by the Gray test)(Fig. 1).

There was no effect of etomidate on SOFA scores. SOFA scores for patients treated with etomidate compared to patients who did not receive etomidate were 10 [8–13] and 11 [9–13] (*P* = 0.14) at baseline (Table 1) and at day 7 were 6 [3–10] and 6 [3–9], (*p* = 0.65), respectively. The change in SOFA score from baseline to day 7 for patients treated with etomidate compared to patients who did not receive etomidate were –4 [–6;–2] and –4 [–7;–1] (*P* = 0.36), respectively.

Discussion

This study confirms that a bolus dose of etomidate is associated with an increased incidence of IRC and is also associated with increased mortality in at least one of our models. Hydrocortisone treatment had no effect on outcome in patients who received etomidate.

Use of etomidate

This study documents that etomidate is still widely used in intensive care practice across Europe. Even though the use of etomidate was discouraged in this study, it was still given to more than one quarter of the patients enrolled and 19.2% within 72 h of trial inclusion. Etomidate is still used primarily for its low cardiovascular complication rate during induction of anaesthesia [34, 41]. Despite this potential benefit, there are no studies demonstrating improved outcome over other agents [34, 42]. The use of etomidate for induction of anaesthesia was similar in this

Table 1 Baseline demographics, ACTH response and mortality

Baseline demographics	Etomidate in 72 h (n = 96)	No etomidate in 72 h (n = 403)	All patients (n = 499)
Age (years)	68 [61–74]	64 [52–74]	65 [53–74]
Male gender	64 (66.7)	268 (66.5)	332 (66.5)
SAPS II	49 [37–66]	47 [37–58]	48 [37–60]
SOFA score (baseline)	10 [8–13]	11 [9–13]	10 [9–13]
SOFA cardiovascular component (baseline)	4 [4–4]	4 [4–4]	4 [4–4]
Race—Caucasian	92 (95.8)	372 (92.3)	464 (93.0)
Reason for admission			
Medical	29 (30.2)	145/400 (36.2)	174/496 (35.1)
Elective surgical	12 (12.5)	40/400 (10)	52/496 (10.5)
Emergency surgery	55 (57.3)	215/400 (53.7)	270/496 (54.4)
Cortisol ($\mu\text{g/dl}$); n = 487			
Before administration	20.3 [12.6–32.6]	25.9 [16.7–37.1]	25.1 [16.1–36.1]
After 60 min	30.2 [20.8–37.9]	37.3 [26.5–49.8]	35.5 [25.0–47.7]
Difference	7.2 [1.9–11.3]	9.8 [3.8–16.3]	9.2 [3.3–15.6]
ACTH responders*	37 (38.9)	217 (55.4)	254 (52.2)
Day 28 mortality**	41 (42.7)	123 (30.5)	164 (32.9)
Due to refractory shock	9 (22.0)	42 (34.2)	51 (31.1)
Due to multi-system organ failure	24 (58.5)	55 (44.7)	79 (48.2)
Due to other cause	8 (19.5)	26 (21.1)	34 (20.7)

The table is divided according to whether the patients had received etomidate in the 72 h before trial inclusion, those who did not receive etomidate and all study patients. Data are presented as number (%) or median and [IQR]

* $P = 0.004$ by the chi-square test; ** $P = 0.02$ by the chi-square test

study to the Annane study (26 vs. 24%) [35, 39], but lower than in other studies [30].

Etomidate and inadequate response to corticotropin

The potential for etomidate to induce an IRC has been known for many years [23]. A single bolus dose of etomidate can inhibit steroid metabolism for at least 24–48 h in critically ill patients [15, 22, 25, 43]. Patients given etomidate were at least 12 times more likely to develop an IRC than those not receiving the drug [14, 15, 22, 25]. An association between etomidate and the likelihood of an IRC was found in this study.

Critically ill patients treated with etomidate have been found to have a greater incidence of an IRC [14, 15, 22], and the prognostic importance of adrenal insufficiency in septic shock has been well described [16]. Mohammed et al. [14] retrospectively studied 152 patients with septic shock who had undergone an ACTH stimulation test. Twenty-five percent of the patients received etomidate at some time before the stimulation test, and the incidence of an IRC in these patients was significantly higher than in those who had not received etomidate (76 vs. 51% $P < 0.01$), although numbers were limited.

Etomidate and concurrent steroid therapy

Routine testing of adrenal function has been advocated to guide steroid therapy, and indeed some authorities have

Table 2 Univariate analysis of factors relating to 28 day mortality

Etomidate	28-day mortality (%)	Odds ratio (95%CI)	P-value
All patients			
No	123/400 (30.5%)	1.00	0.02
Yes	41/96 (42.7%)	1.70 (1.07–2.68)	
Hydrocortisone			
No	63/200 (31.5%)	1.00	0.07
Yes	23/51 (45.1%)	1.79 (0.95–3.34)	
Placebo			
No	60/203 (29.6%)	1.00	0.18
Yes	18/45 (40.0%)	1.59 (0.81–3.10)	

Data presented with regard to etomidate administration in all patients, patients who received hydrocortisone and those who received placebo

recommended replacement steroid therapy concurrent to etomidate dosage to counter its known adrenal suppressive effects [8, 9, 16, 39, 42]. It is somewhat surprising that experts would recommend treating the dangerous side effects of one drug by the administration of another with well known and dangerous side effects of its own [42]. An association between etomidate and an IRC was found in this study. Despite this increased incidence of an IRC, there was no evidence for any benefit from hydrocortisone treatment at the dosage used in the study. The lack of effect could be explained by the temporal separation between etomidate and steroid therapy, a wider immunosuppressive action of etomidate not just affecting adrenal 11- β -hydroxylase or the ACTH test evaluating adrenal gland stimulation but not necessarily adrenal

Fig. 1 Cumulative incidence of death (*top*) and shock reversal (*bottom*) within the first 28 days following randomisation. Groups are divided according to previous administration of etomidate in the 72 h before trial inclusion within the two randomised groups

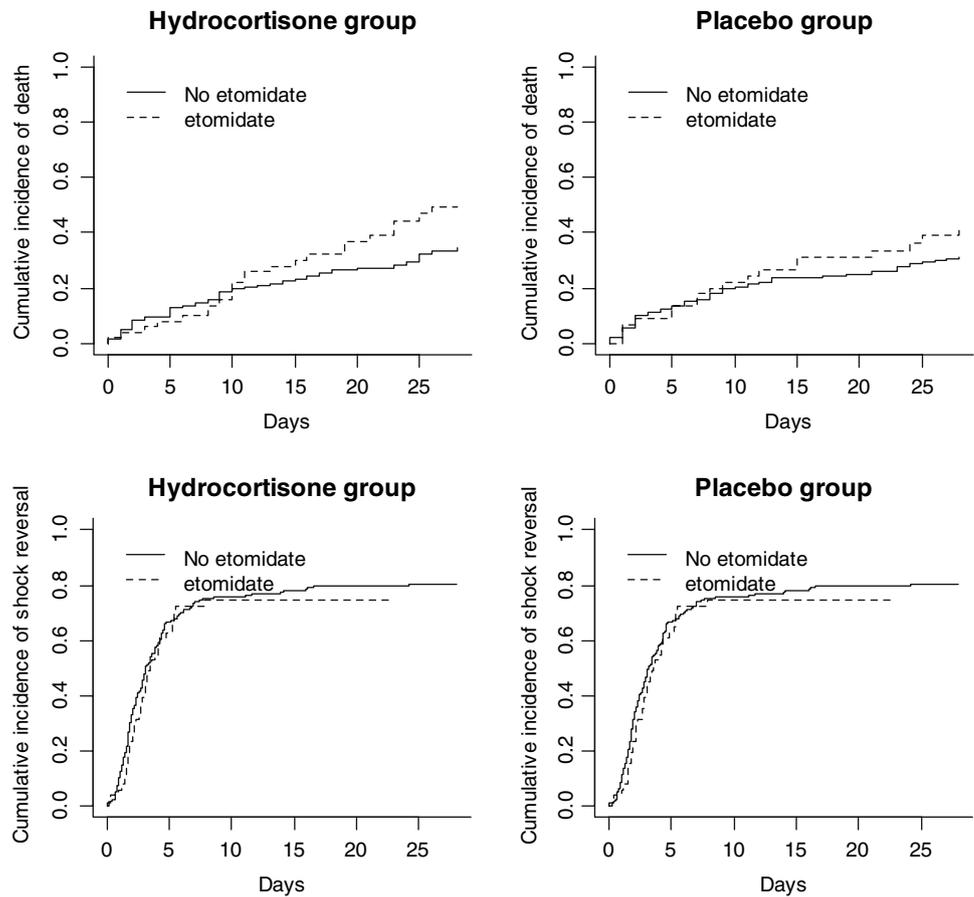


Table 3 Results of multiple regression analyses showing independent predictors of mortality

	Model 1		Model 2	
	OR (95%CI)	P-value	OR (95%CI)	P-value
All patients (n = 487)				
SAPS II	1.03 (1.02–1.04)	<0.0001	1.02 (1.01–1.04)	0.0009
Etomidate	1.60 (0.98–2.62)	0.06	1.75 (1.06–2.90)	0.03
Hydrocortisone group	1.05 (0.70–1.56)	0.81	1.04 (0.69–1.56)	0.84
ACTH non-responder	1.37 (0.91–2.05)	0.13	1.32 (0.87–1.98)	0.19
Baseline cortisol	1.01 (1.00–1.02)	0.045	1.01 (1.00–1.02)	0.04
SOFA	n/a	n/a	1.10 (1.03–1.19)	0.005
Hydrocortisone group (n = 243)				
SAPS II	1.03 (1.01–1.04)	0.005	1.02 (1.00–1.22)	0.05
Etomidate	1.51 (0.77–3.00)	0.23	1.54 (0.77–3.08)	0.22
ACTH non-responder	1.42 (0.81–2.49)	0.22	1.37 (0.78–2.42)	0.28
Baseline cortisol	1.01 (0.99–1.02)	0.18	1.01 (0.99–1.02)	0.22
SOFA	n/a	n/a	1.10 (1.00–1.22)	0.04
Placebo group (n = 244)				
SAPS II	1.04 (1.02–1.06)	<0.0001	1.03 (1.01–1.05)	0.006
Etomidate	1.83 (0.88–3.82)	0.10	2.15 (1.01–4.61)	0.048
ACTH non-responder	1.32 (0.74–2.38)	0.35	1.25 (0.69–2.27)	0.46
Baseline cortisol	1.01 (1.0–1.03)	0.14	1.01 (0.99–1.03)	0.11
SOFA	n/a	n/a	1.11 (1.00–1.24)	0.05

Data presented for risk of mortality in all patients and according to the randomisation group. Logistic regression model 1 adjusts for the treatment group (steroid/placebo), response to corticotropin (responder/non-responder), baseline cortisol value (as continuous variable) and SAPS II score. Model 2 adjusts for these co-variables plus baseline SOFA score

function. This study provides no supportive evidence for the routine use of steroid therapy to treat the adrenal suppressive side effects of etomidate with or without prior corticotropin testing in patients with septic shock. However, it cannot exclude potential benefits from steroid therapy if given immediately after an etomidate bolus, and this area warrants further study. Etomidate also inhibits the synthesis of aldosterone, and the absence of aldosterone replacement may have accounted for the observed lack of steroid benefit.

Etomidate and mortality

This study suggested that etomidate administration was associated with an increased mortality in one of our logistic regression analyses. An obvious hypothesis is that the increased mortality was due to the adrenal suppressive effects of etomidate. It is noted that the Kaplan-Meier curves for mortality do not separate until approximately 10 days after study inclusion. It could be argued that the toxic side-effects of a drug should have a more rapid effect on mortality. Such rapid effects are indeed seen in adrenal responses after etomidate administration. However, this later temporal relationship for death could still be due to the toxic side effects of etomidate, especially if the early adrenal suppressive effect caused by etomidate is the main factor that later leads to the excess mortality. Another possible explanation could be that etomidate was used more commonly in patients with higher severity of illness due to its improved cardiovascular stability. The patients who received etomidate had increased severity of illness (according to SAPS II but not SOFA scores) compared to those who did not receive the drug, but, after correcting for severity of illness, etomidate was still associated with an increased mortality ($P = 0.03$) in one of our models. The analysis of SOFA scores shows no differences in baseline or day 7 SOFA scores or in the change in SOFA score between baseline and day 7 between groups. Further, there was no difference in baseline cardiovascular SOFA scores between groups, so the presence of organ failure is unable to further explain these effects. Perhaps the combination of higher baseline severity of illness and the adrenal effects of etomidate combined to lead to a higher mortality but the mortality effect was delayed. We do not have enough data to explain these observations in the current study or to make a clear hypothesis as to the cause of this observation.

In a retrospective study of 477 septic patients from 20 European ICUs who had undergone an ACTH stimulation test on the day of sepsis onset [30], Lipiner-Friedman et al. showed that 237 (50%) of patients had received etomidate in the 24 h prior to inclusion. Patients receiving etomidate were at increased risk of death on univariate analysis, but the differences were no longer statistically significant on multivariate analysis [30]. There are three

other studies that showed no mortality differences in patients who received etomidate or not [14, 31, 34]. In the study by Mohammed et al. [14] there was no difference in mortality between those who received etomidate and those who did not (63 vs. 55% $P = 0.45$). Riché et al. [31] studied 118 septic shock patients who underwent a laparotomy or drainage for intra-abdominal infection; the 58% who had received etomidate in the 24 h preceding cortisol measurements had a similar mortality as the other patients. Ray et al. [34] reviewed 159 septic shock patients over a 40-month period and found that 46.5% had received etomidate within 24 h of their ICU admission. There was a difference in mortality between patients who received etomidate and those receiving other induction agents (69 vs. 55%), but the differences did not achieve statistical significance. In the study of Annane et al. [6, 9, 39], 68 of the 72 patients (94%) who received etomidate for the induction of anesthesia did not respond to a corticotropin test and had a higher mortality. In the placebo arm, non-responders had a mortality rate of 77% in the etomidate-treated patients and 67% in those who did not receive etomidate (Prof. D. Annane, personal communication). The present results should lead to extreme caution in the use of etomidate in patients with septic shock because of an likely excess mortality. It is unclear whether these results apply to the use of etomidate in other stages of sepsis or in other critical illnesses, but it would seem appropriate to advise marked caution in the use of this drug in such patients.

Etomidate and reversal of shock

An effect of hydrocortisone therapy on time to reversal of shock was seen in the CORTICUS study, although the total number in whom shock was reversed did not differ between groups [35]. However, etomidate did not affect the time to reversal of shock in survivors or the number of survivors who ultimately achieved reversal of shock. It could be hypothesised that etomidate would slow time to reversal of shock or reduce the number of patients who reversed shock due to effects on adrenal hormone levels affecting adrenoceptor function [35]. This suggests an effect of steroids on adrenoceptor function or further mechanisms mediated through a direct interaction with mechanisms producing vascular hyporeactivity or other anti-inflammatory actions [35]. However, regardless of effects on adrenal function, etomidate does not affect the speed of resolution, or number of patients who resolve, their septic shock.

Strengths and limitations

Strengths of this study include the fact that it was a European-wide, investigator-initiated study including 52

ICUs from nine countries. It is the largest study of its kind that reports on the impact of etomidate use in septic shock. A central laboratory was used for measuring cortisol, and quality assurance evaluations revealed few problems. Limitations of the study include the limited power as only 500 patients were enrolled and the fact that this study was a sub-study and was not designed or powered to test the outcomes prospectively. We do not know the patient's severity of illness at the time etomidate was used so cannot say to what degree their severity of illness on trial entry and subsequent outcome was directly influenced by etomidate use. The multivariate approach is limited by the variables included in the analysis, so that other unmeasured variables could have contributed to the final results. Some of these variables are not truly baseline-independent variables as they were measured after etomidate dosage and may have been affected by etomidate (i.e. baseline cortisol and corticotropin test results).

Conclusions

Etomidate treatment is associated with an increased incidence of non-responsiveness to corticotropin in septic shock patients. Patients who received etomidate did have a higher severity of illness, but after correction for severity of illness there is still an increased mortality associated with etomidate administration in one of our models. Importantly, hydrocortisone administration had no effect on outcome in these patients, and therefore the use of hydrocortisone to treat etomidate adrenal insufficiency should be reevaluated. These data raise serious concerns about the use of etomidate in cases of septic shock. We recommend that clinicians demonstrate extreme caution in the use of etomidate in critically ill patients with septic shock because of its association with an IRC and risk of increased mortality.

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the European Commission, Takeda and Eisai Corporation. C.S. reports having been paid lecture fees by Eli Lilly. D.A. has no conflicts of interest. S.C. has no conflicts of interest. M.G. has no conflicts of interest. S.G. has no conflicts of interest. P.-F.L. has received consulting fees from Eli Lilly. J.L.V. has no conflicts of interest. K.F. has no conflicts of interest. M.S. has received consulting fees from Eli Lilly and Ferring. D.P. has received consulting fees from Edwards Life Sciences, Eli Lilly and Hutchinson Technology and grant support from Eli Lilly and Hutchinson Technology. Y.G.W. has no conflicts of interest. There are no other potential conflicts of interest relevant for this article.

Appendix

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