Etomidate for critically ill patients. Pro: yes we can use it
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Etomidate is used to induce anaesthesia in critically ill patients in many environments, including pre-hospital care, in the emergency and critical care departments and in the operating theatre. It has a favourable cardiovascular profile, but its use has courted controversy because it suppresses adrenal function which some believe is associated with worse outcome, particularly in patients with sepsis. Because there is much evidence of harm associated with hypotension in critically ill patients, it is important to use an anaesthetic induction drug which is less likely to cause hypotension. Etomidate undoubtedly causes adrenal suppression, but the clinical consequences of this remain unclear.

Introduction
Etomidate is a drug used intravenously to induce anaesthesia. It is the most cardiovascularly stable intravenous induction drug, with the possible exception of ketamine, and for this reason it is used widely in critically ill patients, including pre-hospital care, in emergency and critical care departments and in emergency anaesthesia. However, its use has courted controversy because of its suppressant effect on adrenal function which some believe is associated with worse outcome. We believe that etomidate remains a useful drug for induction of anaesthesia in the critically ill patient and that concerns about the consequences of its effect on adrenal function may be overstated, with little supporting evidence that it causes harm. In this article, we review the evidence for continuing to use etomidate in the critically ill.

Advantages of etomidate
The major advantage of etomidate is its relative lack of effect on the cardiovascular system. Etomidate does not suppress myocardial function or sympathetic tone. A standard anaesthetic induction dose of 0.3 mg kg⁻¹ produces minimal blood pressure change in healthy patients, those with ischaemic or valvular heart disease and those in American Society of Anaesthesiologists (ASA) physical status grade 3 or more, although the dose may need to be reduced in elderly and critically ill patients. Etomidate has less effect on blood pressure and heart rate than other currently available intravenous induction drugs. This difference is particularly noticeable when compared with propofol, which is associated with a greater degree of hypotension than other drugs, but this difference also exists when compared with thiopental. In critically ill patients, the relative risk of developing hypotension is lower after etomidate than after thiopental or ketamine, and much lower than after propofol or midazolam. Not only is hypotension less likely to occur, management of hypotension related to induction is less intensive. Critically ill patients with hypotension are particularly at risk of developing immediate and severe life-threatening complications at induction and are more likely to die than patients who are normotensive. Patients exposed to hypotension in the emergency department have a significantly increased risk of death during hospitalisation, and the more severe and prolonged the hypotension, the higher is the risk of death. Hypotension is associated with poorer outcome in traumatic brain injury. Hypotension at induction is an independent risk factor for death in anaesthetic practice and intraoperative hypotension might play a role in the development of postoperative ischaemic stroke. Therefore, in critically ill patients, it is important to use an induction drug which is less likely to cause hypotension. For this reason, etomidate is used widely in several countries in Europe and North America, particularly in pre-hospital physician-delivered rapid sequence induction, in emergency departments.
Disadvantages of etomidate

Apart from relatively minor adverse effects such as pain on injection, nausea, vomiting and occasional excitatory movements, the main problem with etomidate is adrenocortical suppression. Etomidate inhibits 11β-hydroxylase activity, resulting in lower production of cortisol (and to a lesser extent corticosterone and aldosterone). Such suppression occurs after etomidate given by continuous infusion,22 single bolus dose23 and even sub-anaesthetic doses24 and lasts at least 24 h25–29 and possibly up to 72 h.30 The diagnosis of adrenal suppression usually depends on demonstrating an impaired cortisol response to corticotrophin,51 although less commonly an absolute reduction in cortisol or 11β-hydroxylase concentration is used.27,29 Confirming this diagnosis in critical illness is more difficult because corticotrophin stimulation tests may be unreliable.32,33 Etomidate is not the only potential cause of adrenal suppression in the critically ill30; adrenal suppression occurs in 9 to 76% of etomidate-free septic patients32,34,35 compared with 57 to 94% in septic patients given etomidate.34 Although there is clear evidence that etomidate causes adrenal suppression,35–39 it does not occur in every patient given etomidate and the clinical consequences of this suppression are not clear. Corticosteroid replacement therapy to non-septic patients given etomidate does not improve outcome,29 but there are conflicting data about the effect on outcome in septic patients.8,30,39 Concern over etomidate-induced adrenal suppression has led to condemnation of etomidate use,40,41 firm rebuttals42–44 and overviews acknowledging both the advantages and disadvantages of the drug.45–48

Is there any evidence that etomidate causes harm?

Effect on mortality

Several studies suggest that etomidate is associated with increased mortality,26,28,33,37,39,49,50 particularly in patients with severe sepsis or septic shock.28,33,39,49,50 Many other studies have found no relationship between etomidate and outcome.7–9,18,27,29,36,51–57 The first suggestion of possible harm came from a case series of critically injured trauma patients who were sedated using an etomidate infusion in an ICU during the early 1980s.58 In that ICU during 1979 and 1980, when routine sedation consisted of bolus doses or infusions of opioids with or without intermittent doses of benzodiazepine, mortality was 28%, similar to that over the previous 10 years. During 1981 and 1982, this sedation regimen was replaced by etomidate infusion; mortality in this cohort was 77%. After etomidate use was abandoned, mortality reduced to 25%. At first sight, this appears to provide compelling evidence for the deleterious effect of etomidate. However there are several things to consider about this article. Data were gathered retrospectively, etomidate was administered by continuous infusion ‘...in a dose sufficient to maintain sleep, more or less uninterruptedly...' and no patient had any test of adrenocortical function performed. The authors admit that patients who received etomidate were likely to have had a greater depth of anaesthesia than those given opioids and benzodiazepines in the earlier and later cohorts, and that this could have contributed to increased mortality. It is now well recognised that greater depth of sedation in critically ill patients is associated with increased mortality.59 Because of these significant limitations, we should not rely solely on data from this early study to condemn the use of etomidate in critically ill patients.

What about the effect of single bolus doses of etomidate in critically ill patients? Several studies have suggested an association between the use of a single dose of etomidate and increased mortality.26,28,33,38,39,49,50 In 2002, Annane et al.60 reported that low-dose corticosteroid therapy significantly reduced the risk of death in patients with septic shock and relative adrenal insufficiency. Initially during patient recruitment, use of etomidate was not considered a contraindication to inclusion; however, almost 2 years into the conduct of the study, by which time 72 patients had been given etomidate, eligibility criteria were amended to exclude patients given etomidate. Adrenal insufficiency was more common in patients given etomidate than in etomidate-free patients (94 vs. 71%) and mortality in non-responders to a corticotrophin stimulation test who received etomidate was higher in those who received placebo than in those given supplemental corticosteroids (76 vs. 55%). The mortality among patients given etomidate in this study has never been published by the original authors, although the lead author subsequently called for ICU physicians to abandon the use of etomidate.40 Data from a personal communication in a recent systematic review of the effect of etomidate in critical illness34 show that mortality was lower in patients given etomidate than in etomidate-free patients (53 vs. 59%). In the prospective, multicentre Corticosteroid Therapy of Septic Shock study (CORTICUS)33 the induction drug was not randomised but etomidate was actively discouraged; despite this, 96 patients (19%) were given etomidate. A post-hoc analysis suggested that patients given etomidate had a greater risk of death (P=0.03).33 Cuthbertson et al.39 used data from CORTICUS in an a priori substudy to assess this further. Mortality at 28 days in patients given etomidate was 42.7% compared with 30.5% in patients given a different induction drug. On univariate analysis, this translated to an increased risk of death in those given etomidate [odds ratio 1.70, 95% confidence interval (CI) 1.07 to 2.68; P = 0.02],
although patients given etomidate were more severely ill than those given other induction drugs.

In contrast, two prospective, nonrandomised studies of septic patients\textsuperscript{51,52} found no difference in outcome. Riché \textit{et al.} \textsuperscript{51} studied 118 patients with septic shock of abdominal origin and found a mortality rate of 36\% in patients given etomidate compared with 46\% for those who did not receive etomidate. Tekwani \textit{et al.} \textsuperscript{52} studied 106 patients with sepsis criteria in the emergency department, 74 of whom were given etomidate, and found no difference in mortality in patients given etomidate (38 vs. 44\%). Additionally, two retrospective studies of patients with septic shock found no difference in outcome of patients given etomidate.\textsuperscript{5,55} In two further studies, one involving 405 patients in a general ICU who underwent corticotrophin testing,\textsuperscript{36} and the other a study of 137 patients who had rapid sequence induction performed in a level I trauma centre,\textsuperscript{26} outcome for patients given etomidate was no different to that for etomidate-free patients.

Jabre \textit{et al.} \textsuperscript{18} performed a randomised, controlled, single-blind study to compare early and 28-day morbidity after a single dose of etomidate or ketamine used for emergency tracheal intubation in 469 critically ill patients. Although adrenal insufficiency was more common in patients given etomidate, 28-day mortality was not different between the groups (etomidate 35\%, ketamine 31\%; \(P = 0.36\)). The authors’ conclusion that ‘ketamine is a safe and valuable alternative to etomidate for intubation in critically ill patients, particularly in septic patients’ can easily be interpreted as indicating that etomidate is as good as ketamine for tracheal intubation in the critically ill.

A recent, well conducted systematic review and meta-analysis examined the effect of etomidate on mortality in the critically ill.\textsuperscript{34} Twenty-one articles (of which 19 had independent datasets) were evaluated and outcome was reported in 14 of these studies. Authors of primary trials were contacted to identify any unpublished data, quality of studies was considered appropriately, datasets from substudies using the same patients were analysed as one series and statistical weighting in the meta-analysis was given to larger studies. Compared with other induction drugs, etomidate was associated with an increased risk of death (relative risk 1.19, 95\% CI 1.10 to 1.30; \(P < 0.0001\)). This increased mortality remained when only studies of patients with severe sepsis or septic shock were included (relative risk 1.22, 95\% CI 1.11 to 1.35; \(P < 0.0001\)), but there was no difference in mortality when only studies of non-septic patients were included (relative risk 1.15, 95\% CI 0.97 to 1.35; \(P = 0.10\)). The main problem with this meta-analysis is the generally low quality of the studies available for evaluation. Only three randomised controlled trials were included, the rest being observational studies, many of which were retrospective chart reviews, and some studies had very small sample sizes. Furthermore, the study with the largest statistical weighting,\textsuperscript{50} which contributed almost one-third of the data for analysis, was composed mainly of patients who had already been included in other published studies, raising the possibility that some patients were included twice in the meta-analysis. Additionally, the study by Tekwani \textit{et al.}\textsuperscript{52} was not included in the subgroup meta-analysis of septic patients despite their patients appearing to meet the criteria for having sepsis. The results from this systematic review should therefore be interpreted cautiously.

Since the publication of this meta-analysis, three further studies have been published on the effect of etomidate on outcome in septic patients.\textsuperscript{53,54,57} None of these studies found that the use of etomidate was associated with increased mortality. In a randomised, controlled trial, Tekwani \textit{et al.}\textsuperscript{57} compared the effects of etomidate and midazolam on outcome in 122 patients with suspected sepsis. In-hospital mortality was 43\% for those given etomidate and 36\% for patients given midazolam. Ninety-six of the 122 patients had confirmed sepsis, 45 of whom received etomidate; there was also no difference in this subgroup between patients given etomidate and those who received midazolam [42 (95\% CI 28 to 58\%) vs. 33\% (95\% CI 21 to 48\%)]. In a retrospective chart review of 230 patients, in-hospital mortality was 43.9\% in the 173 patients given etomidate compared with 45.6\% in those who did not receive etomidate.\textsuperscript{54} In the other study of 224 patients, Dmello \textit{et al.}\textsuperscript{51} found a relative risk for death of 0.92 (95\% CI 0.74 to 1.14; \(P = 0.51\)) in the 113 patients given etomidate.

Consequently, there are now 18 studies with independent datasets which report mortality after etomidate. In nine of these, patients given etomidate had greater mortality, although statistically significant differences were found in only four.\textsuperscript{7,26,39,50} In the remaining nine studies, no association with worse outcome was found. If the subgroup meta-analysis of Albert \textit{et al.}\textsuperscript{34} is re-analysed without statistical weighting but adding the data from the three new studies\textsuperscript{53,54,57} and from the retrospective study of Tekwani \textit{et al.}\textsuperscript{52} the risk ratio for death in patients given etomidate reduces to 1.10 (95\% CI 1.00 to 1.21) which hardly provides definitive evidence of harm.

Because of its favourable cardiovascular profile, etomidate may be used more often in sicker patients who are more likely to die. This is certainly true in some of the studies included in the meta-analysis\textsuperscript{34}; patients given etomidate were either sicker,\textsuperscript{7,26,39} older\textsuperscript{7} or both.\textsuperscript{7} In a study of induction drug use and outcome of patients admitted to an ICU after emergency laparotomy, there was no association between induction drug and dying in hospital; ASA physical status was the only independent predictor of outcome.\textsuperscript{9} Choice of induction drug was, however, related to severity of illness – the likelihood of using etomidate increased as ASA physical status
worsened (odds ratio 2.2, 95% CI 1.4 to 3.6; \(P = 0.001\)). In the CORTICUS study, patients given etomidate were sicker than those who received a different induction drug.\(^9\) After adjusting for severity of illness, etomidate was associated with increased mortality but only in one of the two models used; the methodology used to construct these models has been criticised.\(^{8,9}\) In two other studies which took into consideration the pre-existing risk of death, there was no difference in outcome of patients given etomidate in the emergency department\(^7\) or of patients with septic shock given etomidate.\(^8\)

Taken together, the results of all these studies cast considerable doubt on the true impact of etomidate on the risk of death. Etomidate is often used in sicker patients who are more likely to die (and was even used in one study in which its use was actively discouraged). There is no convincing evidence that etomidate is associated with increased mortality, particularly in non-septic patients and when adjustment is made for pre-existing severity of illness.

**Effect on vasopressor use, duration of mechanical ventilation and ICU and hospital length of stay**

A consequence of etomidate-induced adrenal suppression in critically ill patients could be a greater need for vasopressor therapy. Only one study,\(^60\) has found this although this was not reported in the original article, but in subsequent correspondence\(^30\): ‘...the day following etomidate, compared to 177 etomidate-free patients they required more fluid loading ...and greater amount of vasopressors (\(P<0.001\)) to maintain cardiovascular homeostasis’. In that study of patients with septic shock, the vasopressor used most commonly was dopamine [273 of 299 patients (91%)] and noradrenaline was used in less than one-third of patients. In five other studies which have reported vasopressor use, no difference was found between patients given etomidate and those given a different induction drug.\(^8,18,52–54\) Indeed, in the study by Ray and McKeown\(^7\) of patients with septic shock, not only was there no difference in the percentage of patients given vasopressors for each induction drug, there was also no difference in total, averaged or maximum dose or duration of vasopressor therapy.

One study found that patients given etomidate had a longer duration of mechanical ventilation, and longer stays in ICU and hospital.\(^38\) In this prospective, randomised study of 61 trauma patients, only 30 were enrolled and included in analysis, 18 of whom were given etomidate. The injury severity score was greater in those given etomidate (26.5 vs. 19.9), although this difference was not statistically significant. Overall mortality was low (7%) and was not different between the groups. These findings are difficult to interpret meaningfully because of the large number of excluded patients and very small sample size. In contrast, a prospective, randomised study of septic patients given either etomidate (\(n = 63\)) or midazolam (\(n = 59\)) found no difference in ventilator days, or length of ICU or hospital stay.\(^57\) Five other studies with larger sample sizes totalling 1094 patients\(^{18,52–55}\) and one other small study\(^61\) found no difference in length of ICU\(^{18,53–55,61}\) or hospital stay\(^{52,61}\) or duration of mechanical ventilation.\(^{18,53,54,61}\)

**Conclusion**

There is much (and increasing) evidence of harm associated with hypotension in critically ill patients. Etomidate offers a clear benefit of improved cardiovascular stability and reduced risk of hypotension at induction of anaesthesia. Etomidate undoubtedly causes adrenal suppression, but the clinical consequences of this remain unclear. There is no convincing or consistent evidence that etomidate is associated with increased risk of death, greater vasopressor use or duration of mechanical ventilation, or longer ICU or hospital stay, particularly if adjustment is made for pre-existing severity of illness. Unfortunately, the effect of etomidate on outcome has never been studied prospectively in a large population of surgical or critically ill patients, and all studies of patients with severe sepsis or septic shock have been underpowered to detect a difference in mortality. The etomidate debate is currently in clinical equipoise in which there is genuine uncertainty within the expert medical community.\(^62\) Practitioners should continue to use the induction drug which they consider is most suitable for the individual patient in the particular circumstance or environment. Etomidate can be used in critically ill patients, particularly those without sepsis. The deleterious effects of hypotension at induction, for which there is clear evidence of harm, are more important than the still unclear consequences of transient adrenal suppression.

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