The role of etomidate as an anaesthetic induction agent for critically ill patients

Etomidate is an anaesthetic induction agent which may be favoured in critically ill patients because of its cardiovascular stability. However, etomidate causes adrenocortical suppression which may be particularly harmful in these patients. This article reviews current evidence and debates the use of etomidate in critical illness.

Etomidate is a short-acting intravenous anaesthetic agent which has been widely used for induction of anaesthesia because of its associated haemodynamic stability. Etomidate is an ester and a carboxylated imidazole. Its structure is shown in *Figure 1*. It was found to have sedative effects during its development as an antifungal agent and was introduced as a hypnotic in Europe in 1972.

The mechanism of etomidate's sedative effect involves binding to two sites on the gamma aminobutyric acid (GABA) type A receptor and potentiating the effect of GABA. Etomidate is also an agonist at central alpha-2 receptors. Vascular tone and myocardial contractility are therefore maintained following an anaesthetic induction dose of etomidate, with minimal changes in heart rate or blood pressure. Etomidate is metabolized by hepatic esterases and then excreted, primarily by the kidney.

Etomidate has been demonstrated to cause adrenal suppression, and there is some evidence suggesting an association with increased morbidity and mortality. The haemodynamic stability associated with etomidate makes it a potentially advantageous agent for induction of anaesthesia in critically ill patients, for example those with sepsis. It is these patients, however, who may be at a greater risk of harm from the adrenal suppression associated with the use of etomidate.

The hypothalamic–pituitary–adrenal axis

The hypothalamic–pituitary–adrenal axis is part of the neuroendocrine system and involves interactions and feedback mechanisms between the hypothalamus, the anterior pituitary gland and the adrenal glands. It plays an important role in the body's response to stress and also regulates many homeostatic processes.

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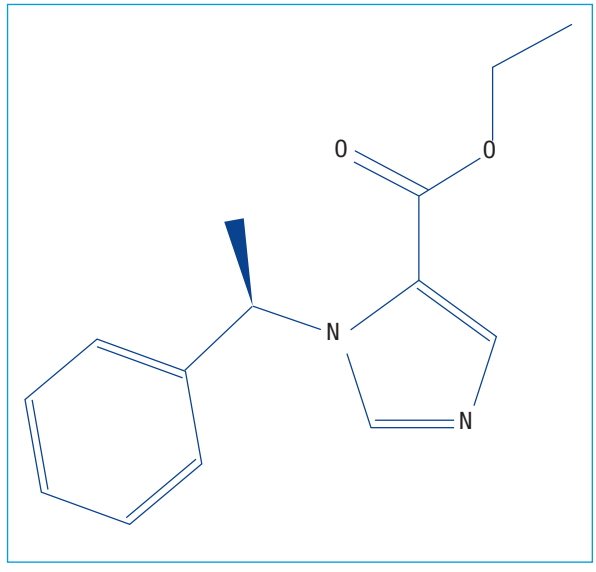
Figure 1. Structure of etomidate.

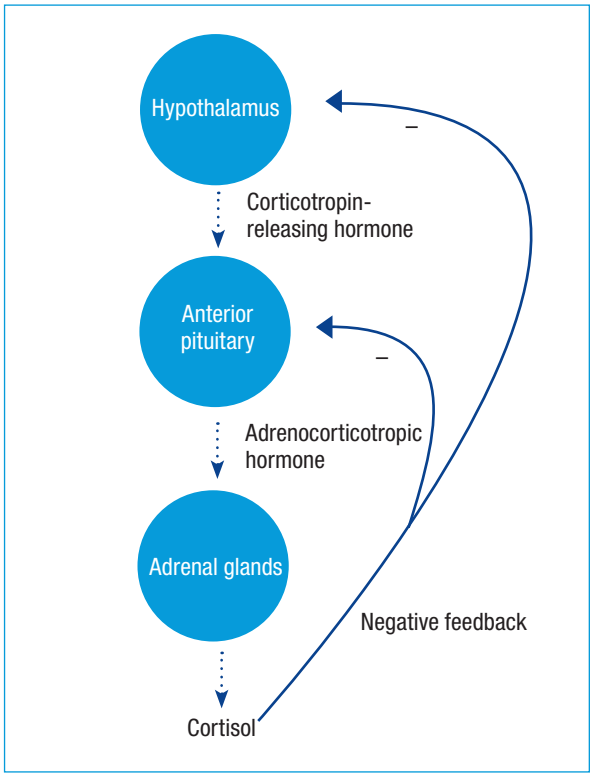


The hypothalamic–pituitary–adrenal axis is demonstrated in *Figure 2*. The key elements are:

- The paraventricular nucleus of the hypothalamus (here neuroendocrine cells synthesize and secrete corticotropin-releasing hormone and vasopressin)
- The anterior lobe of the pituitary gland (here corticotropin-releasing hormone and vasopressin stimulate the secretion of adrenocorticotropic hormone)
- The adrenal cortex (adrenocorticotropic hormone stimulates the production of glucocorticoid hormones such as cortisol)
- Negative feedback mechanisms (glucocorticoids have a negative feedback action on the hypothalamus and anterior pituitary to suppress corticotropin-releasing hormone and adrenocorticotropic hormone production).

The hypothalamic–pituitary–adrenal axis plays an important role in response to infection and sepsis. The system is activated as part of the initial inflammatory response and cortisol is released. Cortisol modulates the synthesis and release of both pro- and anti-inflammatory mediators to restrict inflammation in infected tissues (Annane, 2008). Cortisol levels, however, may be inadequate to control the inflammatory response and

Figure 2. The hypothalamic–pituitary–adrenal axis.



meet the elevated metabolic demand which occurs in sepsis (Marik et al, 2008). This is termed 'relative adrenal insufficiency' and is associated with a poor prognosis in sepsis (Annane et al, 2000). This prompted clinical trials to investigate the role of steroid replacement therapy in sepsis, but the issue remains controversial with trials showing conflicting results (Annane et al, 2002; Sprung et al, 2008). Steroid replacement therapy is therefore often reserved for patients with septic shock who have vasopressor resistant hypotension.

With evidence suggesting an association between adrenal insufficiency and increased mortality in sepsis, it could be construed that patients with sepsis would be at risk of harm from the adrenal suppression caused by etomidate, although the evidence surrounding this is conflicting. This article reviews the characteristics of etomidate and examines the evidence surrounding its use in critically ill patients.

Characteristics of etomidate

Etomidate has many favourable characteristics, making it a suitable agent for induction of anaesthesia in critically unwell patients. It has a rapid onset and will induce anaesthesia within one arm–brain circulation. It also has a short duration of action, which is primarily the result of redistribution. It therefore lends itself to use as part of a rapid sequence induction. It causes less hypotension than other induction agents and is therefore useful when inducing anaesthesia in critically unwell, haemodynamically unstable patients (Oglesby, 2004). Ensuring haemodynamic stability in these patients is vitally important, as there is evidence that even a single episode of hypotension may be associated with poor outcome (Jones et al, 2006). The cardiovascular stability associated with etomidate was well demonstrated by a study comparing propofol to etomidate while using bispectral index to monitor depth of anaesthesia during induction. Although lower doses of propofol were needed, propofol still resulted in significantly more hypotension than etomidate (Möller and Kamenik, 2013).

Etomidate may be advantageous in patients with traumatic brain injury, where the importance of maintaining an adequate cerebral perfusion pressure has been widely demonstrated (Jeremitsky et al, 2003). Etomidate resembles most other induction agents in that it lowers intracranial pressure. Other agents, however, have a tendency to cause a simultaneous reduction in mean arterial pressure and therefore lower the cerebral perfusion pressure. Mean arterial pressure is usually maintained when etomidate is used, resulting in a beneficial increase in cerebral perfusion pressure. Etomidate, like other induction agents, also offers additional cerebral protection by causing a reduction in cerebral metabolic rate.

There are many additional benefits of etomidate: it causes minimal histamine release, allergy is very rare and it causes only limited suppression of ventilation. It also has a wide therapeutic index compared to thiopentone and propofol, meaning there is a wide margin of safety between the therapeutic and the toxic dose.

Etomidate does have some unfavourable characteristics. It was traditionally formulated in propylene glycol and could cause significant pain on injection and venous irritation. This has now been virtually eliminated by the development of a lipid formulation (Mayer et al, 1996). The use of etomidate is associated with an increase risk of postoperative nausea and vomiting. This was quantified by a double-blinded, controlled trial comparing etomidate in lipid emulsion to propofol, which demonstrated that etomidate was associated with an increased incidence of vomiting in women (27% *vs* 10%), but did not increase postoperative nausea (St Pierre et al, 2000).

Etomidate can cause excitatory movements in up to 86% of patients, with myoclonus occurring in 69%. It can cause spikes in electroencephalographic activity and should be used in caution in patients with epilepsy (Reddy et al, 1993). Finally, etomidate is not generally used as an induction agent for elective procedures which leads to a lack of familiarity with its use.

The use of etomidate in critically ill patients

Concern began about an association between etomidate and mortality in 1983 following a letter from Ledingham and Watt (1983) in the *Lancet*. The authors described an observed increase in mortality rate in trauma patients since addition of etomidate to sedation regimens, despite no change in injury severity score. The increase in mortality was the result of multi-organ failure which was invariably associated with intractable sepsis. The authors postulated that the increase in mortality could be the result of

adrenal insufficiency caused by etomidate, which had been demonstrated in rats. Following publication of this letter the manufacturers of etomidate advised that it should no longer be used for prolonged infusion. After discontinuation of etomidate, the authors noted that their mortality rate returned to baseline (Watt and Ledingham, 1984).

Etomidate has since been demonstrated to cause adrenal suppression through inhibition of 11-beta-hydroxylase, an enzyme which plays a key role in steroidogenesis (Wagner and White, 1984). Although no longer used for infusions, etomidate may still be given as a single dose to induce anaesthesia, and there is clear evidence that even a single dose will result in adrenal suppression. Adrenal suppression occurs in both adults and children, and in patients with and without sepsis (Den Brinker et al, 2008). Etomidate causes both absolute and relative adrenal suppression at a plasma level much lower than that required to induce anaesthesia (Allolio et al, 1985; Malerba et al, 2005; Mohammad et al, 2006). The adrenal suppression is fully reversible and can last for 12–48 hours after a single dose (Vinclair et al, 2008).

The safety of a single induction dose of etomidate remains a subject of debate, with some studies suggesting that even one dose could increase morbidity and mortality in critically ill patients. Patients with trauma and sepsis are of particular concern as the normal physiological stress response involving activation of the hypothalamic–pituitary–adrenal axis may be blunted after etomidate, resulting in delayed hypotension. It is these patients who may be most likely to receive etomidate, as a result of the perceived benefit of its short-term haemodynamic stability. As previously discussed, there is evidence to suggest adrenal suppression may be particularly harmful in patients with sepsis, with studies having demonstrated that a reduced adrenal response to a cortisol stimulation test was associated with increased mortality (Annane et al, 2000).

There was increasing concern about the use of etomidate in sepsis following publication of an 'a priori' subgroup analysis of the CORTICUS trial (Sprung et al, 2008), a large randomized, double-blind, placebo-controlled trial which examined the use of hydrocortisone in sepsis. A subgroup analysis of the 19% of patients in the CORTICUS study who received etomidate was conducted in 2009 by Cuthbertson et al. The authors demonstrated that patients who had received etomidate were less likely to respond to hydrocortisone and had a higher mortality. It is possible, however, that unreported patient factors could have accounted for the associated increase in mortality. The study was of insufficient power for this particular analysis, and patients in this subset were not randomized for this purpose; the results should therefore be interpreted with caution.

However, prospective studies have also suggested worse outcomes with etomidate. A meta-analysis by Chan et al (2012) examined the use of etomidate in patients with severe sepsis and septic shock. The review included randomized controlled trials and observational studies, and included 865 subjects. The authors found that etomidate was associated with adrenal suppression and increased all-cause mortality. A systematic review by Albert et al (2011) examined the effect of single dose etomidate compared to other anaesthestic agents. This study also found that etomidate use was associated with increased rates of adrenal insufficiency and mortality. A subgroup analysis showed that the increase in mortality was maintained in the subset of patients with sepsis, but not in the subset without sepsis.

A randomized controlled trial of 30 trauma patients compared outcomes of patients given etomidate and suxamethonium to those given fentanyl, midazolam and suxamethonium (Hildreth et al, 2008). The groups had no significant difference in age, injury severity score or baseline cortisol level. Etomidate was associated with adrenal suppression, and also associated with a significant increase in the length of hospital and intensive care stay and increased ventilator days.

These findings have been confirmed in some retrospective studies. In an observational study Komatsu et al (2013) retrospectively reviewed records of patients with an American Society of Anesthesiologists physical status score (ASA score) of 3–4 who had undergone elective non-cardiac surgery. They compared 2144 patients who had received etomidate to 5233 propensity matched patients who had received propofol, and demonstrated an increased risk of 28-day mortality, increased length of stay and increased major cardiovascular morbidity with etomidate.

The increased mortality which has been demonstrated in these studies has been attributed to adrenal suppression, although this remains speculative. Some work has been done to investigate whether steroid replacement would improve outcome in these patients, but benefits have not yet been demonstrated. In their subgroup analysis of the CORTICUS trial, Cuthbertson et al (2009) found that in patients who had received etomidate, hydrocortisone administration did not influence mortality. Payen et al (2012) conducted a randomized controlled trial of patients without septic shock who were given etomidate. The authors compared patients who received a 42-hour hydrocortisone infusion to controls who received saline. They found that steroid administration reduced the duration of vasopressor support, but did not alter duration of mechanical ventilation, intensive care unit length of stay, or 28-day mortality.

Although evidence suggests that etomidate may be associated with worse patient outcomes, many high quality studies have failed to replicate this finding. In 2009, Jabre et al conducted a large randomized controlled trial comparing induction of anaesthesia with etomidate to that with ketamine. The trial included 469 patients requiring rapid sequence induction in the emergency department. No difference was demonstrated between the two groups in the primary end point of maximum sequential organ failure assessment (SOFA) score during the first 3 days in intensive care, or the secondary end points of 28-day mortality, catecholamine use, median ventilator-free days

and median hospital-free days. There was also no significant difference in intubation conditions between the groups. A further a priori analysis was performed on a subgroup of patients with sepsis and trauma. This again showed no significant differences in morbidity or mortality between the two groups.

A further randomized controlled trial was performed by Morel et al (2011) which compared etomidate to propofol in 100 patients undergoing elective cardiac surgery. They found that a single bolus of etomidate resulted in relative adrenal insufficiency, demonstrated by a significant reduction in response to corticotropin stimulation testing at 12, 24 and 48 hours post dose. They found, however, that there was no associated increase in vasopressor requirements and no significant difference in hospital stay, intensive care unit stay, postoperative troponin levels or hospital mortality. Etomidate was also compared to midazolam by Tekwani et al (2010). This prospective randomized trial of 122 patients with suspected sepsis found no significant difference in mean length of hospital stay or intensive care unit stay, ventilator days or in-hospital mortality between groups.

In addition to these prospective trials, there are also multiple retrospective studies showing etomidate is not associated with worse outcomes. A large retrospective cohort study by McPhee et al (2013) examined 2014 adults with sepsis, severe sepsis or septic shock – 1102 patients receiving etomidate were compared to 912 receiving alternative induction agents, with similar demographics and illness severity. Etomidate was not associated with increased mortality or other adverse outcomes including intensive care unit length of stay, hospital length of stay, vasopressor use and duration of mechanical ventilation. Multiple smaller retrospective studies have compared etomidate to alternative agents, including studies comparing propensity matched groups. These have echoed the findings of the above study and demonstrated that etomidate is not associated with any increase in morbidity or mortality (Ray and McKeown, 2007; Ehrman et al, 2011; Alday et al, 2014).

The future

There have been attempts to develop derivatives of etomidate with improved characteristics by chemically modifying the molecule. 5-Methoxycarbonyl-etomidate, also known as MOC-etomidate, is a modification of etomidate which can undergo rapid ester hydrolysis. When used in rats, 30 minutes after administration of MOC-etomidate there was no reduction in the adrenocorticotropic hormone-stimulated serum corticosterone concentration, whereas an equipotent dose of etomidate caused a significant reduction (Cotten et al, 2009). This may be advantageous in single injections, but use as an infusion may still be problematic. Carboetomidate is an alternative derivate. The etomidate molecule has been modified by removal of nitrogen atom which binds to 11Bhydroxylase. It maintains a hypnotic effect, yet the magnitude of adrenocortical inhibition is greatly reduced (Sneyd and Rigby-Jones, 2010).

KEY POINTS

- Etomidate is an anaesthetic induction agent which is associated with cardiovascular stability and may provide short-term benefit when inducing anaesthesia in critically ill patients.
- Etomidate causes suppression of the adrenocortical axis, which plays an important role in the physiological response to stress and illness.
- There is conflicting evidence about whether a bolus dose of etomidate may cause an increase in patient mortality.
- There are alternative induction agents available which offer cardiovascular stability without the theoretical risk of harm associated with etomidate.
- The future of etomidate may lie in development of derivatives which maintain its favourable features but do not cause adrenal suppression.

Conclusions

There is strong evidence that etomidate causes adrenal suppression, but the effect of a single bolus on patient mortality remains unclear. Many of the studies suggesting increased mortality with etomidate are observational in nature, and therefore must be interpreted with caution. A large meta-analysis has added to the evidence of an increase in mortality, but this is yet to be confirmed with adequately powered randomized controlled trials.

There are alternative induction agents available which offer many of the same benefits of etomidate without the theoretical risk of harm. Without clear evidence confirming the superiority of etomidate it may be that its future lies in development of derivatives which maintain its favourable features but do not cause adrenal suppression. **BJHM**

Conflict of interest: none.

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