

## Editorial

### Etomidate for emergency anaesthesia; mad, bad and dangerous to know?

In the United Kingdom over the period 2001/02, a total of 20 130 deaths within 30 days of surgery were reported to NCEPOD (National Confidential Enquiry into Patient Outcomes and Deaths) [1]. Of these deaths, 15.8% followed non-elective surgery (i.e. urgent or emergency), although this proportion was nearer 25% for certain specialties such as trauma, orthopaedics, vascular and neurosurgery. Similarly, in the placebo limb of a recent study of high risk patients undergoing major elective surgery, mortality rates were 17% [2]. Many factors have been implicated as contributing to peri-operative mortality and morbidity, but has the anaesthetic induction agent etomidate largely escaped scrutiny? For many anaesthetists, and increasingly emergency physicians and prehospital paramedic teams, etomidate is the drug of choice in 'high risk patients'. We seriously question whether its reputation for safety in emergency anaesthesia is justified and if it should continue to be used in any practice.

The carboxylated imidazole anaesthetic agent etomidate was synthesised in 1964 and introduced into practice in 1972. It rapidly gained a reputation as an agent for use in shocked or haemodynamically unstable patients; the ideal or at least the least hazardous induction agent for use in emergency anaesthesia. Etomidate is most commonly used in Europe but it has been withdrawn in the United States, Australia, Canada and the Republic of Ireland, and concerns have been raised previously regarding its use in anaesthesia [3–5] and in the intensive care unit [6]. Countries with licence for use of etomidate include Albania, Austria, Belgium, Brazil, Chile, Colombia, Croatia, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Jordan, Lebanon,

Macedonia, Malaysia, Mexico, Netherlands, Paraguay, Poland, Portugal, Slovenia, Slovakia, South Africa, Spain, Taiwan, Turkey and United Kingdom (personal communication Anuca Somasekaram, Medical Information Assistant, Jansen Cilag UK).

While soluble in water, etomidate is chemically unstable as such and was formulated in the United Kingdom in 35% propylene glycol (Hypnomidate<sup>®</sup>, Janssen Cilag, High Wycombe, UK). This hyperosmolar formulation has been associated with thrombophlebitis and pain on injection in approximately one quarter of patients [7] and with haemolysis [8]. A lipid formulation (Lipuro, Braun, Sheffield, UK) has been developed to reduce these effects and has renewed interest in the drug [6, 9]. Following intravenous bolus administration (0.3 mg.kg<sup>-1</sup>), onset of anaesthesia is compatible with rapid sequence induction and securing the airway in an emergency. Clinical duration is short, principally due to re-distribution, but this may be prolonged with concurrent use of fentanyl. Other adverse effects are common and include myoclonus, dystonic reactions and nausea and vomiting (in up to one-third of patients). Despite these problems, which have limited its use in elective circumstances, etomidate has been popular due to its relative cardiovascular stability. Following bolus administration for induction of anaesthesia, cardiac output and inotropy, systemic vascular resistance and arterial pressure are all well maintained [10, 11].

However, it is well recognised that etomidate inhibits the mitochondrial 11  $\beta$  hydroxylase enzyme of the adrenal steroid synthesis pathway [12, 13]. In the elective situation and among otherwise healthy patients who do not subsequently develop critical illness, adrenal suppression is relatively short lived and has not been associated with adverse outcomes, although there are limited data to confirm this [14, 15]. However, insights into the full implications of

these effects come from studies suggesting suppression persisting for at least 24 h following cardiac surgery [16] and amongst critically ill patients, where a single dose of etomidate suppressed a cortisol increment  $>200$  nmol.l<sup>-1</sup> for 24 h [17] and in the emergency room where etomidate suppressed early corticotrophin testing [18]. Among elective patients undergoing gynaecological surgery the cortisol response to surgery was absent at 48 h after a single bolus of etomidate [19].

While prolonged infusions of etomidate have been evaluated as a sedative regimen in the ICU, a moratorium has been placed on this practice following a substantial increase in mortality (28% to 77%,  $p < 0.0005$ ) among multiply injured trauma patients; mortality returned to 25% when etomidate was discontinued [20]. Among patients who survived beyond 5 days, a clear relationship between depressed cortisol levels and etomidate use emerged, with all patients having at least one random cortisol concentration  $<260$  nmol.l<sup>-1</sup> and 10/17 (58.8%) having at least one  $<100$  nmol.l<sup>-1</sup>. By contrast, all 170 patients not receiving etomidate achieved random cortisol concentrations  $>260$  nmol.l<sup>-1</sup>. Similarly, inotrope requirements were four times higher in the etomidate group (20% vs. 81%) and, in the same unit, cortisol replacement in severely stressed patients on etomidate infusions was found to improve outcome [21]. Perhaps less well known is the use of etomidate as therapy for Cushing's syndrome; not only is etomidate associated with impaired production in times of critical illness, but it is so effective that it can suppress ectopic hypersecretion [22, 23].

The understanding of the adrenal axis during critical illness has undergone considerable developments in recent years. Following 'stress', i.e. shock, trauma, sepsis and surgery itself, elevated levels of cortisol ( $>500$  nmol.l<sup>-1</sup>) are seen almost universally, with the

highest levels being an independent predictor of adverse outcomes [24]. The exact incidence of adrenal insufficiency during critical illness depends upon how adrenal function is investigated, e.g. random cortisol [25], 250 µg corticotropin (Synacthen® or tetracosactin) [26], 'mini-Synacthen® test' (1–5 µg bolus) [27]. Controversy may exist regarding total plasma levels of cortisol considering the reduced corticosteroid binding globulin levels in critical illness [28]; however, what has been established is that, following a variety of insults, the adrenal axis and/or cyclic responsiveness is at least blunted. What has also emerged, at least in the setting of sepsis and septic shock, is that 'low dose', 'stress dose' or 'physiological' doses of hydrocortisone [26] have been associated with reduced mortality, reduced organ dysfunction, improved pressor and catecholamine responses and reduced requirements, and shorter ICU stay [29, 30]. In the largest study to date, this benefit was restricted to patients with an increment  $< 250 \text{ nmol.l}^{-1}$  following 250 µg corticotropin [26]. Physiological doses of hydrocortisone are now a grade C recommendation from the Surviving Sepsis Campaign in the presence of catecholamine dependent septic shock [31]. Meta-analyses from the Annane groups [32, 33] support the use of low dose steroid replacement among pressor dependent septic shock patients. Beyond sepsis, steroid tone is being reconsidered in clinical practice, such as the use of methylprednisolone for non-resolving fibrotic ARDS [34–36].

It is important to anticipate adrenal suppression lasting considerably longer in critical illness than the 24 h seen in otherwise healthy patients given etomidate; this may be close to reproducing the excess mortality associated with infusions of etomidate [21]. The 'gap' in the story is a prospective investigation and demonstration of induction bolus etomidate administration, suppressed steroidogenesis and increased mortality. However, we believe that the onus is on advocates of etomidate to demonstrate its safety as an induction agent for the critically ill when a prolonged infusion is so clearly associated with increased mortality.

Many clinicians point out that they have never experienced problems with etomidate. This is falsely reassuring: the drug is indeed very stable at induction but the consequences for the patient of adrenal suppression impact in the ICU or HDU may occur days afterwards. There is the option of either starting steroid supplementation [37] or testing for adrenal insufficiency following etomidate administration; the former simply acknowledging the inadequacies associated with etomidate and the latter opening a whole new can of worms, not the least of which is the lack of consensus on defining acute adrenal insufficiency.

It may appear a strange time for anaesthetists to call for an anaesthetic agent to be removed from the drug cupboard [38] given the diminishing choice of agents in recent times, but it is our belief that the excess mortality associated with infusions of etomidate, coupled with our improved understanding of corticosteroid tone in critical illness and stress, mandates a critical re-appraisal of the use of etomidate. Furthermore, etomidate is not the only option for stable induction of anaesthesia. Thiopentone is an extremely predictable and stable drug for emergency induction and anaesthetists have extensive experience with it; indeed, it performs very favourably in comparison with etomidate [39]. Similarly, for true emergency induction of anaesthesia, in conditions such as ruptured abdominal aortic aneurysm, ketamine is an excellent choice, with emergence phenomena made largely irrelevant with postoperative intensive care sedation.

In summary, adrenal suppression is well recognised following etomidate, used both as an infusion and as a bolus for induction of anaesthesia, and is associated with excess mortality and morbidity in a variety of acute illnesses. The use of this drug for 'emergency cases' or potentially unstable patients is especially worrying since it is typically in the setting of critical illness (e.g. sepsis and septic shock, inotrope or pressor dependency, hypovolaemia) that adrenal suppression is devastating. Perioperative adrenal insufficiency and its

consequences among patients on long-term steroid therapy are well recognised and feared. Conversely, the ability of single doses of etomidate to produce adrenal insufficiency is largely neglected. In the absence (and with little prospect) of an adequately powered prospective study with follow up long enough to identify postoperative adrenal failure, a number of options exist. Perhaps NCEPOD with its follow up to 30 days should consider induction agents used. Certainly, if etomidate is administered one should regard patients at risk of adrenal suppression and manage them as such. It is not clear whether serial testing of adrenal function or routine administration of steroids are safe alternatives, particularly considering the delays in test results and lack of consensus in interpretation. We therefore believe that it is unacceptable to administer etomidate blindly to critically ill patients and would suggest that clinicians stop using etomidate forthwith, in any formulation, for emergency and high risk cases and use a less hazardous alternative instead.

C. Morris

Specialist Registrar Anaesthesia  
Ulster Hospital, Dundonald, Belfast,  
Northern Ireland  
E-mail: cmorris@doctors.org.uk

C. McAllister

Consultant Anaesthetist  
Craigavon Area Hospital, Craigavon,  
Northern Ireland

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