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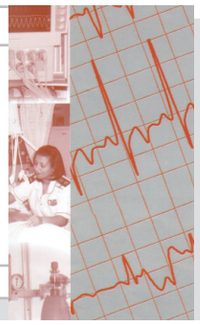
Avoiding etomidate for emergency intubation: throwing the baby out with the bathwater?



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Introduction. Recent literature questions the suitability of etomidate as a rapid-sequence intubation (RSI) drug, owing to induced relative adrenal insufficiency (AI) and possible increased mortality.

Aim. This paper examines the evidence for and against etomidate in the shocked emergency patient and whether or not its use should be cautiously considered or abandoned in this patient cohort, given the AI effect. The issue is examined from the perspective of the **septic shock** patient, the **child** and the **trauma** patient.

Method. A literature review focusing on the risk-benefit ratio and whether there are mortality differences in the outcome of patients in whom etomidate is used, that are attributable to the relative adrenal suppression with even a single bolus dose.

Discussion. The evidence of relative AI is clear, but the cause-effect relationship of increased mortality is not as clear. Currently, most evidence is in the context of septic shock, with only retrospective studies in the trauma subgroup, with a small or moderate sample size.

Conclusion. Etomidate should preferably be avoided as an RSI drug in the septic patient, and cautiously considered in the trauma patient, provided that steroid supplementation is provided in the event that vasopressor-resistant shock occurs.

The aim of this paper is to critically examine etomidate and the indications for its use as an emergency induction agent in the light of recent literature (specifically in the trauma patient), with the intention of providing best-evidence guidelines for this patient subgroup.

As a result of recent evidence that even a single bolus dose of etomidate may suppress adrenal cortical function, leading to a relative adrenal insufficiency (AI),[1-6] there has been extensive debate in the recent literature, with numerous editorials discussing the safety of etomidate (Hypnomidate; Janssen SA) in patients requiring a rapid-sequence intubation (RSI). Opponents of the use of etomidate have called for total avoidance of the drug in the shocked patient, based on the presumed increase in mortality attributable to etomidate in patients in whom the drug was used. Etomidate is, however, a cardio-stable drug with many advantages in the emergency setting over a number of the other rapid-sequence intubation induction agents, such as propofol and thiopentone. It would be prudent to examine the evidence carefully before throwing the 'baby' (etomidate) out with the 'bathwater' (putative evidence to avoid this drug in all shocked patients in emergency departments).

Etomidate is a rapid-acting anaesthetic induction agent with a short half-life that is considered safe in pregnancy. The most common side-effects are pain on injection and myoclonus, which are reduced by concomitant administration of opioids or benzodiazepines. Relative adrenal suppression is well described. Bolus doses are recommended; continuous infusion for sedation has been discouraged since the late 1980s.[7-10]

Method and materials

A literature review, using a Medline search, was undertaken, utilising the search terms: etomidate, trauma, sepsis, adrenal insufficiency and outcome, including the entire available electronic Medline database from 1966 to 2008. Thirty-eight relevant papers, editorials, letters to editors and other articles were identified and reviewed in the context of the questions posed below.

The main question that this paper sets out to answer is whether the disadvantage of adrenal suppression (absolute or relative) outweighs the advantages of using etomidate in the emergency RSI of shocked trauma patients. The historical reasons against

pg. 13-25.indd 14

Table I. **Prospective studies (randomised or otherwise) examining etomidate and/or including relative AI**

Study, publication year and reference number	Setting	Number of patients	Primary endpoint and finding	Mortality	AI incidence: etomidate v. other
Den Brinker, 2005[30]	Observational cohort study in children with meningococcaemia	69	Adrenal function comparing non-survivors, shock survivor and sepsis survivors	Non-survivors had higher SOFA scores and interleukin-6 levels and % intubated with etomidate	Bolus etomidate had high association with AI (88% v. 37%)
Plewa, 1997[37]	Trauma ED intubations	20	Cardiovascular changes	Not included	Mentioned, not evaluated
Absolom, 1999[15]	Randomised clinical trial etomidate v. thiopentone in anaesthesia for critical illness	35	Response to ACTH test: more patients had poor ACTH response if given etomidate	Higher in non-responders to ACTH in both groups	More AI in etomidate group
Deitch, 2003[36]	Pre-hospital prospective observational trial of RSI for trauma	36	BP before and after drug administration; intubation ease. Only 9% incidence of hypotensive episodes after drug administration	Not evaluated	Not evaluated
Choi, 2004[35]	Prospective phased observational trial of etomidate v. midazolam in ED	160	Hypotensive episodes: More after midazolam than etomidate	Not discussed	Not evaluated
Cohan, 2005[25]	Prospective evaluation of AI in head-injured (TBI) v. non-head-injured in trauma ICU	121 (80 TBI) No AI data for non-TBI group presented	Incidence of AI: 53% of TBI patients had AI	No difference	AI higher incidence if etomidate used (p=0002) – not sustained after 24 hours
Malerba, 2005[16]	University ICU: factors associated with AI in cases of severe sepsis of septic shock	62	Non-response to ACTH test: generally in sicker patients who received etomidate. 30% of non-responders did not receive etomidate	Mortality higher in non-responders (70.4% v. 31.4%)	Only etomidate significant for AI after multivariate analysis

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Table I. (continued) **Prospective studies (randomised or otherwise) examining etomidate and/or including relative AI**

Study, publication year and reference number	Setting	Number of patients	Primary endpoint and finding	Mortality	AI incidence: etomidate v. other
Zed, 2006[24]	Prospective observational trial in university ED	522	Intubation conditions and haemodynamic changes: 80% good intubation conditions with 96% adequate sedation and no haemodynamically significant compromise	14 deaths all in cases of severely ill patients with cardiac arrest before or during etomidate administration	Not evaluated
Zuckerbraun, 2006[31]	Paediatric tertiary ED: drug efficacy and safety	77 (32 trauma and 15 other shock)	Good intubation conditions in 99%. Haemodynamics remained stable. No difference for the shock sub-group	3 deaths all due to massive head or multiple system trauma. Etomidate did not appear to influence mortality	8 patients received steroids for shock. Presumed AI. Total cortisol levels were low in 6
Sprung, 2008[10]	Multi-centre, PRCT double blind in ICU primarily examining the role of steroids for septic shock. Etomidate was one variable examined	499	Difference in outcome with or without steroids in septic shock	No mortality difference if given steroids or placebo	Mortality 9% higher if non-responder irrespective if given etomidate, provided they received steroids

ED = emergency department.
SOFA = sequential organ failure score.

Results and discussion

Historical background

Tables I and II provide an overview of several studies and the significant results. The use of etomidate by constant infusion in ICUs as a sedation agent for ventilated patients was abandoned in 1984 because of evidence of increased mortality owing to reversible adrenal suppression.[8,9] Ledingham, in charge of the ICU of the Glasgow Royal Infirmary, kept a comprehensive database, and noticed an increase in mortality after the introduction of continuous infusions of etomidate in comparison with bolus administration. Ledingham's group published their findings in 1987[32] and restated them in 1990.[33] Their evidence is presented concerning the relative reversible adrenal suppression after bolus dose administration of etomidate. The presence of adrenal suppression in traumatic and non-traumatic shock is examined in patients receiving etomidate, and specifically the extent of adrenal suppression in the two groups. The question of the suitability of etomidate in children is investigated. The final aspect of this paper is to collate all the evidence into a best-practice guideline for the role of etomidate in modern RSI protocols and to consider whether additional steps/therapies in all these patients are required or not.

pg. 13-25.indd 15 7/22/08 2:09:33 PM

pg. 13-25.indd 16

Table II. **Retrospective studies (matched groups or otherwise) examining etomidate as emergency drug or influence on AI**

Study, publication year and reference number	Setting	Number of patients	Primary endpoint and finding	Mortality	AI incidence: etomidate v. other
Migden, 1998[38]	ED case series and personal insights	20	Adverse events: No significant adverse events and muscle relaxant recommended in trauma cases	Not mentioned	Not mentioned
Sokolove, 2000[29]	2 academic medical centres, consecutive patients without comparator drug	100 consecutive children (72 trauma)	Hypotensive episodes or AI after etomidate: 96.2% had no hypotension episodes. No AI recognised as an indication for steroid supplementation	Not mentioned	No AI after use of etomidate throughout hospital stay in these children
Guldner, 2003[28]	University ED retrospective record review	101	BP changes, drug profile and adverse events: Average increase in BP by 4SBP/7DBP mmHg. 4% incidence of vomiting. 38 patients required steroids. Only 1 for sepsis, rest for swelling or asthma. No AI documented	3 – all related to head trauma	None detected in the records – ACTH tests not routinely performed
Swanson, 2004[34]	Prehospital air medical programme etomidate v. midazolam for RSI in patients >15 years of age	210 (76% trauma)	Intubation success and haemodynamic changes: Minimal differences in haemodynamics between the two drugs, but midazolam doses were very low. Both 98% success of intubation	Not mentioned	Not assessed

7/22/08 2:09:34 PM

pg. 13-25.indd 18

Table II. (continued) **Retrospective studies (matched groups or otherwise) examining etomidate as emergency drug or influence on AI**

Study, publication year and reference number	Setting	Number of patients	Primary endpoint and finding	Mortality	AI incidence: etomidate v. other
Price, 2005[41]	Academic trauma ICU: Retrospective analysis of consecutive patients	22 trauma patients who had received etomidate in prior 36 hours	Incidence of AI: 41% of group had AI. Time to test (before or after 18 hours post-dose) did not influence result	Not mentioned	9 AI
Beeman, 2005[39]	Community hospital retrospective chart review of trauma patients ISS 13 or more: Presence of AI	267	AI diagnosed as vasopressor-dependent shock or electrolyte abnormalities: Only 8 (3%) patients developed AI	0/8 with AI died	1/8 with AI had received etomidate
Mohammad, 2006[22]	Tertiary hospital: septic shock association with AI after etomidate	152	AI in association with etomidate. 76% AI with etomidate v. 51% AI without etomidate	No mortality difference	Higher incidence (by 25%) of AI in those receiving etomidate
Lipiner-Friedman, 2007[20]	20 European ICUs: Severe sepsis/septic shock	477 who had ACTH test (only 19 trauma). 237 received etomidate	Non-response to ACTH stimulation test or lower total cortisol levels and AI compared with outcome	Patients receiving etomidate and no steroids had increased mortality risk. 169 of 286 deaths in non-responder group Etomidate OR for mortality was 1.53	289 had AI. Etomidate increased use in ACTH non-responders
Cotton, 2008[19]	Trauma registry review academic trauma centre	137 patients who underwent ACTH test: 83 non-responders	Identification of and risk factors for AI in trauma. Haemorrhagic shock, vasopressor requirement and etomidate use higher in non-responder group. Etomidate is a modifiable risk factor	29 died, no difference between those who were responders or non-responders (19% v. 23%)	71% of patients receiving etomidate v. 52% of patients not receiving etomidate were non-responders to ACTH (p=0.03)

ED = emergency department.
OR = operating room.

7/22/08 2:09:34 PM

of etomidate for sedation. Initially, it seemed to be the ideal sedation agent as it was haemodynamically stable and rapidly reversible.

The withdrawal of etomidate infusions in the ICU led to a reduction in overall mortality; the difference in mortality was significant. The initial report by Fellows and associates[8] demonstrated in a group of 6 patients that etomidate infusions caused suppression of the responsiveness to short tetracosactrin tests, which reversed after discontinuation of the etomidate and recurred after the drug was recommenced. This report was followed by the much larger retrospective review from Watt and Ledingham,[9] which clearly demonstrated a mortality difference between those patients receiving no etomidate infusions (28%) and those who received etomidate (77%). The increased mortality rate in the ICU decreased to the baseline (25%) after discontinuing etomidate infusions. There is clear evidence not only that etomidate as an infusion suppresses adrenal function, but that it also increases mortality.

What is the degree of relative adrenal insufficiency in the patient receiving a bolus dose of etomidate?

Etomidate, even in bolus doses, has been known to reversibly suppress adrenal cortical function causing a relative AI,[11] but this has not been considered sufficiently clinically significant to avoid use of the drug in emergency care because the serum cortisol levels remained at normal limits and the cosyntropin stimulation test results returned to normal at or soon after 24 hours.[12] The small numbers of patients in the reports and lack of placebo controls limited the importance of these studies.

Recent literature, however, has questioned whether the effect on mortality has not been underestimated, particularly in the ICU environment. What **is** highlighted in these articles, which include editorial correspondence articles and primary research papers,[1-5,10,13-20] is that the majority of patients in all the studies demonstrating the presence of AI were cases of **septic shock** (the underlying septic pathology), while very limited research is available to justify the extension of the policy of avoiding etomidate in other forms of shock or critical illness.[21]

It is interesting to note that in one study where etomidate was identified as a factor contributing to AI, the authors avoided the use of a midazolam infusion for patient sedation, citing evidence that this drug may also blunt the adrenal stress response.[15] They also stated that no patient (in their group of 35 patients) had absolute adrenal failure; they comprised mainly surgical patients, but no trauma patients. Interestingly, the comparator drug thiopentone also apparently had an effect on adrenal function (12% of patients in this group had AI), while significantly less so than etomidate (29%). It was not stated whether there were particular reasons for the use of etomidate instead of thiopentone, thus making it impossible to assess clinical decision-making as a factor in drug choice. There was, however, no **mortality** difference between the groups – although this may be related to the sample size. There was also no statistically significant difference in cortisol levels between the groups at any time.

In a larger study of 62 patients, Malerba *et al*.[16] tested the hypothesis that etomidate was an independent factor in AI. They prospectively followed patients in the ICU and assessed outcomes after 28 of the patients had received etomidate as their induction agent for intubation in the ICU. They found that non-responders to a short corticotrophin test (no increase in cortisol after administration of adrenocorticotropic hormone (ACTH) were more likely to have been given etomidate (19/27 v. 9/35 not given etomidate). There was a statistically significant difference in survival when comparing corticotrophin test responders with non-responders, but it was not further explained in their paper whether the non-responders who died had all been given etomidate or not. They called for more studies with a higher power to further appraise the risk-benefit ratio of the use of etomidate – and noted that patients receiving etomidate were 'generally sicker' than those who did not! This may imply that underlying pathology dictates the use of a more stable drug, and therefore the underlying pathology may actually be causing the AI.

In the accompanying editorial to the Malerbe article in *Intensive Care Medicine*,[1] Annane pointed out that it had been determined that a standard dose of 0.3 mg/kg of etomidate can inhibit the synthesis of corticosteroid hormones for about 5 hours. He observed that the risk of AI in the study had been increased 12 times by the use of etomidate, proving that this drug affects the outcomes of critically ill patients. On the other hand, he clearly stated that etomidate was but one factor in a multifactorial disease process in critically ill patients. He recommended alternative drugs, such as dexmedetomidine, that may not be available in some countries and are primarily for sedation, rather than induction and intubation.

Following from that editorial, Bloomfield and Annane exchanged a number of comments in letters addressed to the correspondence columns of *Intensive Care Medicine and Critical Care Medicine*.[2-4] Bloomfield advocated the routine use of low-dose steroid supplementation in all patients admitted after having already received etomidate in the emergency department. Annane concurred with this advice and cautioned again that this treatment is in the context of septic shock, stating that there was now no doubt that there is an acute and often sustained AI in septic shock. What one cannot support is Annane's contention later in the reply that he would suspect that the same would be true of other critically ill patients, as he

provides no evidence to support this contention. He also provided data, albeit unpublished, that there were more factors than just etomidate as causes of AI in the non-responder group.[3] Annane further pointed out in his reply that the use of etomidate had **no effect on overall survival** in the studies they had published[17,18] and that the mortality rates were significantly different in the group given steroid supplementation irrespective of whether etomidate was used or not.

Murray and Marik,[5] in their editorial comment on Jackson's literature review[21] regarding the use of etomidate in septic patients, pointed out that, while relative AI is common after etomidate use, the effect on outcome is less clear, the mortality cost of the AI resulting from etomidate being offset completely in those given low-dose steroid therapy, by its benefits in the induction phase being readily apparent. Jackson[21] went on to point out that overt irreversible AI had not been demonstrated in any study till that time. He highlighted the fact that many of the studies available were limited by sample size, patient selection and procedure type, and that the tests used to determine the AI were neither uniform nor standardised. Less than 200 patients were included in all the studies combined. No study in this group showed a negative effect on mortality. In assessing the benefits of etomidate in this group of critically ill patients, Jackson[21] indicated cardiovascular stability as a major benefit. The article emphasised that the evidence applied to cases of septic shock only, and concluded by stating that a state of equipoise existed.

While some evidence suggests that low-dose corticosteroids may be of benefit in cases of septic shock,[17] more recent reports suggest that it only shortens the time of vasopressor dependence, and not survival, making the usefulness inconclusive.[10,20] There is no consensus as to whether AI is caused by etomidate or sustained to the point that it affects outcome in the patients receiving steroids. The recent Corticus study[20] showed that mortality in patients with septic shock, who received etomidate and developed AI, without steroid supplementation, was higher than in the rest of the cohort. Mortality in both the treatment and placebo groups was higher by about 9% in those receiving etomidate. This same subgroup, however, had more patients with etomidate use due to their clinical picture, namely hypotensive shock. The study was, also unfortunately, underpowered by about 300 patients to enable one to truly draw representative conclusions. Once again, there were limited numbers of patients admitted after trauma in the study population of the preceding retrospective study (19 out of 477),[10] and the number of patients who were trauma admissions was not specified in the Corticus randomised study.[20]

A large retrospective study[22] to examine the role of etomidate in AI included 152 patients with septic shock, and demonstrated an AI incidence of 76% in those patients receiving etomidate compared with 51% of those patients who did not receive etomidate; but once again, no statistically significant difference in mortality was found between the two groups. Caution was once again highlighted regarding the use of etomidate in the septic shock group of patients. One must certainly, therefore, consider carefully the benefit of a cardio-stable induction in this group of patients versus the risk of needing to supplement with steroids, with the attendant possible increase in septic complications.

Is relative reversible adrenal suppression after bolus dose etomidate in the shocked patient the same for cases of traumatic and other forms of shock as for cases of septic shock?

All the available data reviewed focus on the septic shock patient.[1-5,13-18,21-23] The question above is whether this applies to all shocked patients equally and whether it affects mortality in any way. While the pathophysiology of the different types of shock is similar, the clinical presentation and effects of therapeutic management (and response to that therapy) are often very different. The available literature revealed only one study where non-septic patients were included; this was a very small study (11 patients) in patients undergoing urgent cardiac revascularisation, and again revealed a mild intra-operative adrenocortical suppression that reversed during the latter part of the surgery and postoperatively, specifically after aortic unclamping.[23] The authors used midazolam as the comparator, which is also known to modulate adrenal response, but they did note a cortisol reduction over time in the etomidate group prior to unclamping. No survival difference was noted.

Is etomidate a suitable emergency induction agent?

In an observational cohort study in Canada, Zed and co-workers examined the effects of etomidate on a large population (491 patients) of emergency intubations at a tertiary hospital emergency department.[24] They noted that intubation conditions were mostly good to excellent after the use of etomidate and that the acute adverse events were likely to be related to underlying pathology rather than the etomidate dose. All intubations were successful. The case mix included trauma, medical, cardiac and neurological disease. They did not specifically investigate AI in their study but noted that, in the acute setting, etomidate was more cardio-stable than thiopentone, propofol and midazolam. Indeed, the mortality of the group (around 3%) was consistent with published reports of emergency department resuscitation mortality. The authors highlight that, in their population, only 5% of the patients had sepsis (although not necessarily septic shock) as an underlying factor, making conclusions about the role of etomidate in subsequent AI difficult.

pg. 13-25.indd 20 7/22/08 2:09:35 PM

Most patients had a favourable haemodynamic profile and indeed a rise in blood pressure from baseline, with eventual pulse decrease.

Cohan and associates from UC-Davis[25] reported on the influence of etomidate on the head-injured patient. They studied the factors that cause secondary AI in traumatic brain injury in 80 head-injured and 41 other trauma patients presenting at their facility. AI was sought by means of cortisol level up to day 9 and by ACTH stimulation testing with 1 µg cosyntropin within 48 hours, as well as after 3 and 6 months. Prior steroid use was an exclusion criterion. The authors found that the group of head-injured patients (64% were shocked on arrival) who received a single dose of etomidate had a higher incidence of AI than those who had not received etomidate (81% v. 58%). All patients who received etomidate had lower mean cortisol levels than those who did not receive etomidate; but there were also higher numbers of patients with hypotension and hypoxia in the etomidate cohort. By the second day after admission, this difference was no longer significant. Other metabolic suppressive agents (thiopentone, propofol) also showed a suppression of cortisol production, although not of statistical significance except in the case of alcohol. The serum cortisol absolute values were slightly lower across the board for those without head injury, and the diurnal variation was lost for both groups. Both groups had a peak ACTH in the first 24 hours post-injury. When AI did occur, it was mostly after day 2 post-injury, with mean daily cortisol levels lower for those with AI, but with similar ACTH levels. While etomidate was identified in univariate analysis as a predisposing factor for AI, this no longer reached statistical significance after multivariate analysis was performed. AI was only weakly shown to influence final outcome at 6 months. In summary, they report that relative AI occurred in 50% of head-injured patients, was central in origin,[25,26] occurred in younger patients, patients with higher severity of injury, and where etomidate had been administered. They also admit that other centrally acting agents (propofol, thiopentone) also decreased cortisol levels. Given that a single dose of etomidate only on the first day post-injury had been administered and that the majority of patients developed AI at 2.4 days post-injury, they felt that the effect of etomidate as a cause of AI was probably minimal. They have since embarked on a prospective randomised trial to evaluate the use of low-dose steroids in the head-injured population who are at risk for AI.[26] Many other studies were identified from the literature search that examined the incidence of AI, but none could be found where the specific relevance to etomidate was examined, and these were therefore excluded from further analysis.

In summary, the evidence is weak that etomidate itself produces life-threatening AI in non-septic shock adult patients, except in the subgroup with severe head trauma, where a central factor may play a role. The drug's other benefits may therefore outweigh the risks, given that the risk is identifiable and treatable. Some of the alternative agents are not without fault, either. Additionally, good evidence exists[27] that high-dose steroids increase mortality in the head-injury group. Physiological-dose steroids may be beneficial in certain patients with septic shock, but the role thereof in traumatic head injury has not been adequately evaluated, and there may be an increased risk of septic complications, even with these lower doses of steroids.

Do the same physiological changes occur in children?

Children differ in their physiology and in the pharmacological metabolism of drugs. The expectation, therefore, is that the effects of etomidate may be different in children, and they may or may not be more prone to AI. Four studies on the use of etomidate in children and the relationship to the effect thereof upon the incidence of AI could be found in the literature.[28-31] One further study examined head-injured children and the effect of etomidate on outcome.[32]

In their study,[28] Guldner's unit actively looked for the presence of AI in all the patients, as they were evaluating the safety of etomidate in the paediatric age group. They also included not only septic patients; 57% of their cohort was trauma cases. All children were under the age of 10 years, and 105 children were included in the study. Only 4 early adverse events in 105 intubations were recorded; 3 of these were vomiting, a well-described side-effect of etomidate. No clinically or laboratory-detected AI was found in their patient cohort. In the discussion, they concluded that the incidence of AI, when including the single previous study,[29] amounted to only 0.5%. All other children receiving steroid therapy in the cohorts were treated for other steroid-sensitive underlying pathologies, and not AI. In children with meningococcal sepsis,[30] the incidence and association with AI was once again similar to data in the septic adult population, with etomidate shown to have suppressed cortisol production, with a decreased production ratio of up to 84%, and specifically reduced 11-beta-hydroxylase enzyme function in the adrenal cortex, a known side-effect of etomidate.

Bias might have occurred, as they did not report on the incidence of ischaemic adrenal necrosis in this patient cohort – a well-described consequence of meningococcaemia.

Increased mortality in the most severely ill children was suggested by the data, but this was not consistent throughout the other subgroups of less severely ill children. The authors cautioned against etomidate intubation in the septic child.

Zuckerbraun and colleagues[31] reviewed 89 patients admitted to their emergency department, 77 of whom received etomidate; 70% of the total cohort was <12

years of age. Trauma was a cause in 41% of admissions. In the cohort, no patients experienced myoclonus. Eight patients were considered to be in decompensated shock, and 15 in compensated shock. There were no differences in this sub-group compared with the rest of the cohort regarding initial response to treatment, but all 8 of the patients who experienced AI were part of this shock sub-group. Six of the 8 had low cortisol levels drawn after etomidate administration, but one was normal, and one that was drawn before the use of etomidate was also low. All 3 deaths that occurred were unrelated to the use of etomidate. In the discussion, the authors noted that first-time intubation success was higher in their study than the earlier study, but they also noted that haemodynamic changes were minimal – even favourable – in the most severely shocked patients. Their study could not answer the question of the exact role of a single dose of etomidate in the pathophysiology of AI.

A small study of etomidate in the head-injured child[32] showed that single-dose etomidate significantly reduced intracranial pressure and improved cerebral perfusion pressure, without altering mean arterial pressure. AI was not evaluated and this evidence is not comparable with the study in adults.[25] Therefore, it appears as if etomidate in children is safe, provided that the indication for intubation is not (once again) septic shock.

Should we use etomidate in the prehospital field or the emergency department for RSI algorithms, given the available evidence; and what alternatives are there that provide equal early intubation success?

Two recent papers[6,33] examined the choice of induction and other agents in either the prehospital or emergency department, listing etomidate as one of the agents, and three papers examined etomidate and/or a comparator drug in emergency intubation.[34-36] A further two scientific letters about the use of etomidate in the trauma scenario specifically, were also identified.[37,38]

Easby and Dodds[33] highlight that the agent of choice in the prehospital setting remains unclear, and that most practitioners use the drugs they are familiar with for RSI. Regarding etomidate, they note the existing literature regarding the septic patient and emphasise that further randomised studies were needed to identify whether the trauma patient and other emergency patients were at equal risk. They also highlight the good overall safety profile compared with some of the other agents, namely the risk of hypotension and cardiovascular collapse with propofol; the hypersalivation and emergence phenomena with ketamine; and hypotension with midazolam if used alone. In the conclusion, they surmise that etomidate has the best safety profile of the currently available drugs.

Oglesby[6] reviewed 16 papers as part of an evidence-based appraisal of etomidate in the emergency department. While much of the article reflects the author's opinion, an interesting point noted the decreased intracranial pressure reported in several papers and, therefore, a potential benefit in the head-injured patient, which could be questioned in the light of the Cohan study.[25] He did, however, emphasise that clinically significant AI after a single dose of etomidate in the emergency department setting had till then not been conclusively documented.

Swanson *et al.*[34] and Choi *et al.*[35] both published comparative studies with midazolam as the comparator drug. Between them, they included 370 patients, with 190 patients receiving etomidate and the rest receiving midazolam. While Swanson found no statistical difference in the intubation successes or in episodes of hypotension with either drug, Choi, using a phased study approach, suggested a statistically significant increase in episodes of hypotension when using midazolam, even in 'low' doses of 2 - 4 mg total doses, compared with etomidate. The jury appears still to be out on the prehospital drug of choice. Deitch *et al.*[36] performed a prospective, observational study with a small sample size of 36 trauma patients and found that only 9% of etomidate recipients experienced transient hypotensive episodes (drop in SBP to less than 90 mmHg after initial SBP >100 mmHg) after induction of anaesthesia. It was not noted whether the cause was related to the drug or to the underlying injuries (ongoing bleeding), but they concluded by supporting the notion that an overall blood pressure improvement had been observed in the context of trauma patients needing RSI.

Plewa and colleagues wrote a scientific letter[37] reporting on their experience with etomidate in trauma patients, and highlighted the fact that, in their small observational series, there were no clinically significant adverse outcomes after single- or two-bolus doses of etomidate. They also noted that the adrenal suppression reported after infusions was the probable reason for the lack of popularity of the agent as an emergency drug at the time of writing (1997). In the following year, a letter from Migden and Reardon[38] to the correspondence section of the same journal not only confirmed the findings of Plewa *et al.*, but also advised etomidate-only induction as a matter of choice in the emergency situation, except for trauma, where they recommended routine muscle relaxation.

Beeman and co-workers[39] reported on the incidence and factors surrounding AI in trauma, and identified only 8 patients (3% of the trauma population) with AI. Only one of these had been intubated with etomidate as the induction agent (personal communication, Brian Beeman). They identified 4 subsequent cases; for only one of these had etomidate been given. They could not identify what percentage of the other 652 non-AI cases had received etomidate. One small prospective

randomised study with only 30 patients was presented in abstract form at the 2007 American Association for the Surgery of Trauma meeting.[40] The patient groups were apparently well matched in terms of age and injury severity score (ISS). While this study showed the presence of adrenal suppression in the trauma group to be present in a significant number of the patients given etomidate relative to those given fentanyl and midazolam, there appeared to be only a significant prolongation of ICU stay, ventilator days and hospital length of stay, but no decrease in survival to discharge in the group given etomidate. One can also criticise the use of ISSs, which may have similar numerical values, despite markedly differing injuries, as it is a poor marker of a good matching of injury severity between the groups. Additionally, the small numbers may make type 2 errors possible in the assessment of this group of patients.

The same can be said for the small study of 22 patients presented by Price and colleagues at the International Symposium on Intensive Care and Emergency Medicine (ISICEM) conference and published in abstract form only.[41] They reviewed the incidence of AI in specifically major trauma patients who had received etomidate within the preceding 36 hours. A 250 µg ACTH stimulation test was performed. Nine patients were identified as non-responders. No difference was noted with regard to dose administered compared with responders. There was also no difference in the number of non-responders before or after 18 hours post-etomidate dose. Caution was advised in checking if etomidate had been used and, if so, to maintain a lower threshold to utilise steroids in this patient cohort.

Lastly, a more recent retrospective cohort study in the trauma subgroup[19] that included a larger study sample (137 patients) was identified, but the study suffers from the fact that it is retrospective in nature. It was demonstrated by the authors that, once again, the group of patients who had haemorrhagic shock on admission, or the need for vasopressors beyond 24 hours, or who had exposure to etomidate more than 24 hours prior to the diagnosis of AI, were all associated with a statistically higher chance of being a 'non-responder' to a corticotrophin stimulation test. The *p*-value was 0.03 for etomidate compared with 0.005 for haemorrhagic shock and 0.002 for the need for vasopressors. However, the authors also considered any patient who **might** have received etomidate within 24 hours prior to the test as having **not** received etomidate (non-exposure). This last criterion may create bias against any real conclusions regarding the safety of etomidate in this patient cohort. There were also a higher number of patients in the 'non-responder' group with adrenal haematoma on computed tomography (CT) scan, which could influence the interpretation of results, although this did not reach statistical significance. Additionally, in the discussion section of the paper, the authors conceded that they neither evaluated the effect of other drugs known to interfere with the hypophysial-pituitary-adrenal axis, such as benzodiazepines, morphine and anticonvulsants, nor did they examine the effect of other induction agents (propofol, midazolam, ketamine or thiopentone) on the development of AI. The 'non-responder' group had longer ICU stay and ventilator days. Finally, there was no statistical difference in mortality between the two groups (19% v. 21%). Again, they called for a prospective randomised control trial to fully evaluate their findings.

The association of increased mortality after AI and etomidate use in trauma patients is therefore inconclusive, and the benefit of the drug may still outweigh its risk, provided that due consideration is given to the early administration of low-dose hydrocortisone (50 mg, 6-hourly for 5 days) to the patient receiving etomidate if they develop vasopressor-dependent shock.

Practical guidelines based on the current literature with specific reference to the traumatic shock subgroup

If trauma patients come to the emergency department and the need for RSI is identified, the following practical suggestions should be followed:

- Assess for the presence of shock.
  - Consider all the risks and benefits of induction agents prior to intubation. If patient shocked, try to resuscitate before intubation is attempted.
- Assess the need for an induction agent.
  - If non-drug intubation possible, proceed with intubation.
  - If drug required for induction, consider the options:
    - etomidate – 0.1 - 0.3 mg/kg IVI
    - morphine 0.2 mg/kg IVI and midazolam 0.2 mg/kg IVI, recognising that the risk for hypotension is higher
    - consider ketamine 2 - 4 mg/kg IVI, recognising the relative risk to the head- and ocular-injured patient, as well as the emergence phenomena, which may cause a problem later
    - all other drugs may decrease blood pressure, excessively increasing hypoperfusion
    - always add muscle relaxant (usually suxamethonium).
- If the instability of the patient necessitates a cardio-stable agent and etomidate is utilised, documentation on the use of etomidate must be clear to enable administration of low-dose steroids if the patient develops vasopressor-dependent shock.

Conclusion

The literature on the use of etomidate has much opinion and limited evidence-based research, most

of which is currently retrospective in nature. What is evident from the literature is that etomidate should probably be avoided in the **septic-shock** patient, although all the current literature is biased by the person doing the intubation selecting etomidate for the haemodynamically unstable patient. The safety of etomidate in other types of shock (in particular, trauma-related shock and head injury) is less clear, although the occurrence of AI has been clearly documented. A mortality difference has **not** been clearly demonstrated to date in the trauma subgroup. There does not currently appear to be enough evidence to suggest avoiding etomidate completely as an emergency induction agent, and the benefits may indeed outweigh the risks of AI, which are small at best and treatable with low-dose corticosteroids at worst if the patient develops vasopressor-dependent shock. The majority of trauma patients will not be septic, unless there is a delay in diagnosis and treatment; rather, they may have contamination of wounds, which are best treated by irrigation and prophylactic doses of antibiotics only.

On the balance of the available evidence, 'the baby' (etomidate) should not be 'thrown out with the bathwater' (total avoidance of etomidate in emergency departments) just yet. What will answer this issue finally will be a randomised trial with a fairly cardio-stable comparator drug, such as ketamine, in trauma patients only, looking at the specific incidence of AI in this patient group.

I have no interest in, nor have I received any benefits from, Janssen Pharmaceuticals.

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