

**REVIEW**

Should etomidate be the induction agent of choice for rapid sequence intubation in the emergency department?

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The ideal induction agent for emergency airway management should be rapidly acting, permit optimum intubating conditions, and be devoid of significant side effects. This review was performed to ascertain whether etomidate should be the induction agent of choice for rapid sequence intubation (RSI) in the emergency department, specifically examining its pharmacology, haemodynamic profile, and adrenocortical effects. A search of Medline (1966–2002), Embase (1980–2002), the Cochrane controlled trials register, and CINAHL was performed. In addition, the major emergency medicine and anaesthesia journals were hand searched for relevant material. Altogether 144 papers were identified of which 16 were relevant. Most studies were observational studies or retrospective reviews with only one double blind randomised controlled trial and one un-blinded randomised controlled trial. Appraisal of the available evidence suggests that etomidate is an effective induction agent for emergency department RSI; it has a rapid onset of anaesthesia and results in haemodynamic stability, even in hypovolaemic patients or those with limited cardiac reserve. Important questions regarding the medium to long term effects on adrenocortical function (even after a single dose) remain unanswered.

Rapid sequence intubation (RSI) is defined as the administration of a potent intravenous induction agent followed immediately by a rapidly acting neuromuscular blocking agent to induce unconsciousness and motor paralysis to facilitate tracheal intubation.1 RSI has become the standard technique for definitive emergency airway management in the emergency department (ED) as it creates optimal conditions for intubation while minimising the risk of pulmonary aspiration.2,3 The commonest agents used for RSI in the ED in the United Kingdom are thiopentone, etomidate, and propofol.4–9 The choice of induction agent in any individual patient is determined by coexistent cardiovascular, intracranial, or reactive airways disease, hypertension or hypotension, or hypovolaemia, as well as the individual physician’s personal preference of agent.10

The ideal induction agent for emergency airway management should be smooth and rapidly acting, permit optimum intubating conditions, and be devoid of cardiovascular, respiratory, and cerebral excitatory side effects.11

No single induction agent meets all these requirements and, as yet, no one drug has emerged as the agent of choice for ED RSI in the UK. All induction agents have the potential to cause myocardial depression and secondary hypotension, depending on the drug chosen, the dose, the speed of administration, and the pre-induction status of the patient.12

Thiopentone, a short acting barbiturate, has been viewed historically as the “gold standard” induction agent for RSI because of its rapid action and efficacy.13–17 It can, however, cause pronounced haemodynamic effects with reduction in arterial pressure, left ventricular stroke work index, and pulmonary wedge pressure. These effects can be profound in patients with pre-existing hypovolaemia or cardiac disease. It causes potent respiratory depression and rapidly diffuses across the blood-brain barrier. Reduction of both cardiac output and arterial blood pressure leads to a secondary reduction in intracranial pressure.18

Propofol, an alklyphenol derivative, provides rapid onset of action and potent attenuation of pharyngeal, laryngeal, and tracheal reflexes.18–21 An important disadvantage of rapid injection of propofol is the considerable reduction in systemic vascular resistance and systemic arterial pressure.19–21

Etomidate is a carboxylated imidazole compound that was introduced in Europe in 1972. It is used increasingly for RSI of ED patients because of its rapid onset of anaesthesia, haemodynamic stability, cerebral protective properties, and lack of respiratory depression.21–26

Walls has claimed that it is “the induction agent of choice” for emergency endotracheal intubation.1

The aim of this review is to consider whether etomidate should be the induction agent of choice for RSI in the ED, specifically examining its pharmacology, haemodynamic profile, and adrenocortical effects.

METHODS

Medline (1966–2002) and Embase (1980–2002) were searched using the search strategy in appendix 1 (available on line http://www.emjonline.com/supplemental). The Cochrane controlled trials register, and CINAHL were also searched.

Abbreviations: RSI, rapid sequence intubation; ED, emergency department

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The bibliographies of relevant articles were hand searched for further references.

In addition, the major emergency medicine and anaesthesia journals (Academic Emergency Medicine, Anaesthesia and Analgesia, Annals of Emergency Medicine, British Journal of Anaesthesia, Emergency Medicine Journal) were hand searched for additional relevant material for the time period January 1997 to June 2002. Abstracts from the Faculty of Accident and Emergency Medicine Annual Conference, London, 2001 and those from the Ninth International Emergency Medicine Conference, Edinburgh, 2002 were examined.

Personal communication with acknowledged experts in the field yielded further information. The frequency with which various induction agents are used for ED RSI was obtained from published data. The basic pharmacology of etomidate was reviewed and the evidence regarding its use in emergency department RSI was appraised.

RESULTS
Altogether 144 papers were identified from the initial Medline, Embase, Cochrane, and CINAHL search of which 16 were relevant. In addition various papers were obtained from manual searching of the bibliographies of relevant studies.

Table 1 shows the use of various induction agents in emergency department RSI. Table 2 shows a summary of the relevant emergency department trials.

Data shown as percentages.

**BASIC PHARMACOLOGY OF ETOMIDATE**

Etomidate induces loss of consciousness rapidly (5–15 seconds) and recovery occurs in 5 to 15 minutes. Its pharmacokinetic characteristics include rapid uptake and rapid clearance. The initial distribution half-life is 29 minutes and the elimination half-life 2.9–5.3 hours. Seventy six per cent is bound to albumin at physiological pH of 7.4. The drug is metabolised by esterase hydrolysis in the plasma and the liver forming etomidate carboxylic acid. The metabolites are excreted in the urine; 2% is excreted unchanged.

**Haemodynamic profile**

The cardiovascular effects of etomidate have been studied extensively in the non-ED setting. In most studies etomidate causes no significant change in haemodynamic status and consistently shows a superior haemodynamic profile compared with thiopentone. Etomidate, when used as the sole induction agent, does not reliably attenuate the haemodynamic response to laryngeal stimulation. Studies have shown that pre-treatment with fentanyl (2–10 µg/kg) attenuates this response. When used in patients with severe left ventricular dysfunction etomidate does not cause significant changes in the haemodynamic state.

**Cerebral protective properties**

Etomidate reduces cerebral blood flow, intracranial pressure, and cerebral oxygen consumption while maintaining arterial blood pressure and cerebral perfusion pressure.

**Adrenocortical suppression**

Etomidate was withdrawn as an agent for continuous intravenous sedation in the intensive care setting as it was shown to increase mortality. Subsequently this was found to be attributable to inhibition of 11-β-hydroxylase activity and adrenocortical suppression.

Controversy exists regarding the adrenocortical effects after a single dose of etomidate. Most studies assessing this are in the non-ED setting in comparatively healthy patients. Clinically significant adrenocortical suppression after a single dose of etomidate in the ED setting has yet to be reported.

**Other effects**

There are a variety of other effects caused by etomidate but few are relevant in the ED setting. Apnoea can occur, this is common to all induction agents. Pain occurs on injection. Nausea and vomiting occur on awakening in 30% to 40% of patients. Hypertonus, coughing, laryngospasm, hiccups, and involuntary muscle movements are reported to occur in 14% to 70% of patients receiving etomidate in non-RSI intubations.

**DISCUSSION OF EMERGENCY DEPARTMENT EVIDENCE**

The ideal induction agent for RSI in the ED should be rapidly acting, avoid awareness, and permit good intubating conditions with minimal haemodynamic disturbance. There are a limited number of studies evaluating the use of etomidate for RSI in the ED setting and each of these will be discussed (see table 2). There was only one double blind randomised controlled trial and one un-blinded randomised controlled trial. The other studies were observational studies or retrospective reviews.

Graham et al (personal communication) reported that 89% of patients undergoing ED RSI in Scotland had “physiological compromise” before intubation. Etomidate was used as the induction agent in 33% of this group. There were 328 patients with head injuries and etomidate was used in 26.2%. There were 70 patients who were hypotensive (systolic blood pressure <90 mm Hg) before RSI. Etomidate was used in 66% of this group of patients.

Overall, the first attempt success rate was significantly higher in the patients who received etomidate (89.3% compared with 80.3%, p = 0.001). Interestingly, however, the complication rate was higher in the group where etomidate was used as the induction agent (14%) than with thiopentone (10%) or propofol (8%). The complications related to technical difficulties as well as to physiological deterioration. They included oesophageal intubation, vomiting and aspiration.

<table>
<thead>
<tr>
<th>Author</th>
<th>Etomidate</th>
<th>Thiopentone</th>
<th>Midazolam/Benzos</th>
<th>Propofol</th>
<th>Opioids</th>
<th>Ketamine</th>
<th>Others</th>
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<td>8.0</td>
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<td>0.8</td>
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<td>21.1</td>
<td>47.8</td>
<td>0</td>
<td>8.9</td>
<td>6.0</td>
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<td>0</td>
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endobronchial intubation, surgical airway, hypotension (systolic blood pressure < 90 mm Hg), and critical desaturation (oxygen saturation < 90%).

Smith et al performed a prospective observational study of RSI using etomidate in an urban level 1 trauma centre. There were no reports of inadequate sedation or difficult intubating conditions. There was no significant change in haemodynamic state after administration of etomidate, even in patients with significant cardiac disease and pre-induction hypotension.

This study has various limitations. It is an observational study in a small (n = 34) convenience sample of patients. There is no blinded comparison with other agents and there is no power calculation. There is no record of the experience of the intubator, the number of attempts, or any complications. Most of the outcome measures are subjective and there is no comment whether they were assessed by the intubator or by an independent assessor.

Swanson et al performed a retrospective review of patients undergoing RSI with etomidate in the aeromedical setting. Over a 13 month period, 53 (67%) patients who were intubated received etomidate for RSI. Trauma accounted for 39 (74%) of total intubations.

There was no significant change in haemodynamic state after induction. Mean decrease in systolic blood pressure was 1.3 mm Hg (95% CI for change in BP = -6.6 to 4.1 mm Hg). Mean decrease in heart rate was 3.5 beats per minute (95% CI for change in HR = -5.8 to -1.3 bpm). This is statistically significant but is not clinically relevant.

Four patients were hypotensive before RSI (defined as systolic blood pressure < 90 mm Hg). After induction the systolic blood pressure increased to greater than 100 mm Hg (three patients) and greater than 90 mm Hg (one patient). Four patients (8.7%) developed hypotension after RSI but this was transient and observed on only one reading in three of the four patients.

The study excluded patients where case notes were incomplete, which may cause bias. There is inadequate information on the patients who underwent surgical airways (n = 2) with respect to diagnosis and why the intubation was difficult. It is unclear why only 42 (79%) patients received suxamethonium. However, valuable information regarding prehospital RSI by trained intubators was obtained.

A further retrospective review by Sokolove et al examined the safety and haemodynamic effects of etomidate for emergency RSI of 100 consecutive paediatric patients.

A single investigator examined patient details, indication for intubation, drug dose, and use of exogenous corticosteroid treatment during hospital stay.

There was no significant change in haemodynamic state after induction. In four patients (4.8%, 95% CI 1.3% to 11.7%) reduction in systolic blood pressure to below one standard deviation of mean normal for age occurred. In two of these patients the hypotension was transient. In one patient the hypotension was probably related to hypovolaemia (liver laceration and pelvic fracture). One patient with a severe closed head injury had persistent hypotension (unexplained by other injuries) and died. No patient required corticosteroids for suspected acute adrenal insufficiency although no attempt was made to directly assess adrenal status or function.

This study had several weaknesses. It was a retrospective review of paediatric RSI with no blinded comparison. Only 53 (54%) patients received suxamethonium (in total, 99% received a muscle relaxant) and there was no distinction between these groups in the results section.

Blood pressure was recorded only once at a mean of 8.5 minutes after intubation. This may have missed some episodes of clinically important hypotension. A post-intubation BP was only recorded in 84 patients (84%).

A commonly cited disadvantage of etomidate is adrenocortical dysfunction. Schenarts et al performed a prospective, randomised, placebo controlled trial to assess whether etomidate use for RSI in the ED was associated with adrenocortical dysfunction.

Randomisation to etomidate or midazolam occurred using a computer generated randomisation table. The primary outcome measure was adrenocortical function as measured by the cosyntropin stimulation test (CST) 4, 12, and 24 hours after induction agent. This comprised a pre-CST cortisol measurement followed by administration of 250 μg of exogenous cosyntropin (synthetic ACTH) and measurement of cortisol one hour later.

At four hours there was a significant difference between groups regarding CST results (normal response in 100% of control patients and 30% of etomidate patients, p = 0.004).
The cortisol values before and after ACTH for all etomidate patients remained within or above the normal cortisol reference range (10–25 μg/100 ml). At 12 and 24 hours there were no significant differences between the groups.

There was no long term follow up of the patients regarding corticosteroid replacement in ICU and the sample size was small (n = 31). It remains unclear whether the administration of a single dose of etomidate in critically ill or injured patients causes any clinically important effects.

EMERGENCY DEPARTMENT STUDIES WITH OTHER INDUCTION AGENTS

There are few ED studies of other induction agents. Sivilotti et al performed a prospective randomised double blind study comparing the haemodynamic effects of thiopentone, midazolam, and fentanyl in RSI. There were no significant differences between the groups in relation to number of intubation attempts or the laryngeal views obtained.

Patients were intubated more rapidly (defined as intubation within 300 seconds of the start of the protocol) in the thiopentone group than in the midazolam or fentanyl groups (p = 0.037). There was a trend to delayed intubation in the midazolam group; this did not attain statistical significance but may be of clinical significance.

In terms of haemodynamic status, thiopentone caused a reflex tachycardia and a moderate reduction in blood pressure. Midazolam gave rise to a moderate tachycardia and a mild hypertensive response to intubation and fentanyl displayed a mild increase in blood pressure but stability in relation to heart rate. Fentanyl seemed to provide the most stable haemodynamic profile during RSI.

EMERGENCY DEPARTMENT ABSTRACTS

A small number of important studies have been published in abstract form only regarding the use of etomidate for RSI in the ED.

Woodward et al retrospectively assessed the haemodynamic effects of etomidate for RSI in trauma patients in the ED. The mean increase in systolic blood pressure was 13 mm Hg (95% CI for change in BP 6 to 20 mm Hg). In the 12 patients with pre-induction hypotension (SBP<110 mm Hg), only one had a further reduction in systolic blood pressure after RSI.

Overall, post-induction systolic blood pressure decreased in 15 (25%) patients (<110 mm Hg in three patients and <90 mm Hg in one). No intervention was required in any patient because of blood pressure changes. Before and after RSI heart rate did not change significantly. In summary etomidate in trauma RSI did not cause haemodynamic instability, even in patients who were hypotensive before induction.

Johnson et al prospectively observed the haemodynamic effects of etomidate. There were no significant changes in non-invasive blood pressure, respiratory rate, or oxygen saturation. Pain at the injection site occurred in three (15%) patients and myoclonus occurred in 13 (70%) patients.

Laurin et al published a retrospective review of the haemodynamic changes and adrenal suppression after ED RSI with etomidate. There were no significant haemodynamic changes after RSI. There were nine complications but it was unlikely that any of these resulted because of adrenal suppression secondary to etomidate.

Plewa et al performed a prospective evaluation of etomidate during RSI of trauma patients in the ED. It had rapid onset and duration of action. There were minimal haemodynamic effects, even in patients with haemodynamic instability before induction.

Choi et al compared the haemodynamic effects of midazolam and etomidate as induction agents for RSI in the ED. They found that midazolam was more likely to cause a significant fall in blood pressure, even when used in low dose, and recommended that etomidate should be used as the agent of choice for RSI in the haemodynamically unstable patient.

Finally, anecdotal evidence from the USA suggests that etomidate is a safe and effective induction agent for ED RSI with a low incidence of induction related hypotension (personal communication with Dr D Birnbaum and Dr V Tayal, USA, July 2002).

CONCLUSION

The evidence regarding the use of etomidate as an induction agent for emergency department RSI is limited, both in number of trials and study design. The available evidence suggests that etomidate is an effective induction agent for ED RSI; it has a rapid onset of anaesthesia and results in haemodynamic stability, even in hypovolaemic patients or those with limited cardiac reserve. Important questions regarding the medium to long term effects on adrenocortical function (even after a single dose) remain unanswered.

It is imperative that further good quality research is performed, comparing the use of etomidate with the other commonly used induction agents in the ED setting.

The development of a national database of emergency department RSI in the United Kingdom will allow an opportunity to study induction agents for RSI, physiological data, and complications.

ACKNOWLEDGEMENTS

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CONTRIBUTORS

Dr A J Oglesby conceived the idea for this review article, performed the literature search, and appraised and summarised the literature available.

REFERENCES

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APPENDIX 1 Search strategy

(modified from the Cochrane filter for randomised controlled trials)

- 1. randomized controlled trial.pt
- 2. controlled clinical trial.pt
- 3. randomised controlled trials/
- 4. random allocation/
- 5. double-blind method/
- 6. single-blind method/
- 7. clinical trial.pt
- 8. exp clinical trials/
- 9. (clin$ adj25 trial$).mp
- 10. ((singl$ or doubl$ or treb$ or tripl$) adj25 (blind$ or mask$)).mp
- 11. placebos/
- 12. placebo$.mp
- 13. random$.mp
- 14. research design/
- 15. (or/1–14)
- 16. animal/ not human/
- 17. 15 not 16
- 18. rapid sequence intubation.mp
- 19. rapid sequence induction.mp
- 20. rsi.mp
- 21. emergency intubation.mp
- 22. 18 or 19 or 20 or 21
- 23. exp etomidate/ or etomidate.mp
• 24. exp thiopental/ or thiopentone.mp
• 25. exp propofol/ or propofol.mp
• 26. exp ketamine/ or ketamine.mp
• 27. exp midazolam/ or midazolam.mp
• 28. induction agent$.mp
• 29. an?esthetic.mp or exp anesthetics, intravenous/
• 30. 23 or 24 or 25 or 26 or 27 or 28 or 29
• 31. 17 and 22 and 30