

Special Report: Should Etomidate Be Used as an Induction Agent for Patients with Sepsis?

No credible evidence supports the assertion that etomidate should be avoided in patients with septic shock.

INTRODUCTION

Etomidate is the most commonly used induction agent in the U.S., and it has gained popularity in Canada.^{1,2,3} However, recent debate about its safety in patients with sepsis has centered around a potential association with adrenal insufficiency.^{4,5,6,7,8} In this special report, we discuss the rationale for etomidate's high utilization, the origins of the debate about adrenal insufficiency, and the current literature regarding the safety of a one-time dose of etomidate in emergency rapid sequence intubation (RSI).

BACKGROUND

Used since 1972, etomidate is an imidazole with hypnotic effects that are thought to be induced through the γ -aminobutyric acid (GABA) adrenergic system.^{9,10} An estimated 80% of U.S. emergency physicians use etomidate for induction during RSI.¹¹ The reasons for high use include rapid onset of action, short duration of action, excellent peri-intubation hemodynamic profile, and relative ease of administration.¹

Combining an induction dose of etomidate with a neuromuscular blocking agent typically produces appropriate intubating conditions within 45 seconds, with a return of consciousness within 15 minutes.¹² Sakles et al. reported the use of etomidate in 491 acutely ill emergency department patients and noted that hemodynamic stability was maintained even in acutely ill hypotensive patients.¹¹ This finding supported those of multiple smaller studies that demonstrated the beneficial hemodynamic profile of etomidate, even in cardiac patients undergoing noncardiac surgery.^{12,13,14,15} Etomidate also has cerebro-protective effects, including reduction of intracranial pressure while maintaining cerebral perfusion pressure.¹⁶ In addition, etomidate does not release histamine and so has no potential to cause or worsen bronchospasm in patients with reactive airways disease.

ETOMIDATE AND ADRENAL INSUFFICIENCY — HOW DID THE CONTROVERSY BEGIN?

Initially, etomidate was used as a continuous sedative for days to weeks in the intensive care unit (ICU), with its popularity driven by its excellent cardiovascular profile. This practice was reevaluated after publication of results of a retrospective study in 428 trauma patients that showed a 23% decrease in mortality after the discontinuation of continuous intravenous infusion of etomidate for sedation.¹⁷ The mortality effect was considered to be secondary to induced

adrenal insufficiency through a concentration-dependent blockade of two cytochrome P450 receptors and 11- β hydroxylase that resulted in inhibition of cortisol production in the adrenal gland.¹⁸ Etomidate is no longer used for continuous sedation.

WHAT IS THE EFFECT OF A SINGLE DOSE OF ETOMIDATE?

The effect of a single dose of etomidate for induction in RSI on subsequent adrenal function is a complicated issue and at the center of heated controversy.^{4,5,6,7,8,19,20,21,22} A review of multiple small studies (in 5–60 patients) demonstrated transient (2–24 hours) adrenal suppression after a one-time bolus dose of etomidate.⁹ This finding is distinct from reports of suppression for up to 3 days after continuous etomidate infusion. In the only trial in the review that involved ED patients, 31 patients undergoing RSI were randomized to receive either etomidate or midazolam as the induction agent, followed by succinylcholine.²³ Adrenocortical response to corticotropin was depressed after 4 hours but had resolved by 12 hours and remained normal throughout the 24-hour study period. No patient had a serum cortisol level below reference values at any time. Although development of some degree of transient depression of adrenal responsiveness to corticotropin after an induction dose of etomidate has been well documented, until recently, only one small study of 35 patients evaluated clinical outcomes. The study reported an association between etomidate and laboratory measures of adrenal insufficiency but no effect on patient outcomes.²⁴

Interest in possible adverse outcomes related to etomidate-induced adrenal insufficiency resurfaced in 2003 after publication of a prospective study of low-dose corticosteroids for patients with septic shock.²⁵ This study demonstrated a 10% absolute mortality benefit for patients treated with IV hydrocortisone and daily fludrocortisone. Because 94% of patients who received etomidate did not respond normally to a corticotropin stimulation test, the protocol was revised 21 months into the study to exclude patients who received etomidate. A post hoc analysis of the 68 study patients who received etomidate for intubation and who did not respond to a corticotropin stimulation test identified mortality rates of 54.8% for patients who had received corticosteroids and 75.7% for those who had received placebo ($P=0.03$).^{2,25} However, no association between etomidate and clinical outcome was reported, making the meaning of this finding unclear.

Etomidate exposure and clinical outcomes were evaluated in the retrospective CORTICUS trial, which was designed to refine the use of baseline cortisol and corticotropin stimulation testing for predicting adrenal insufficiency and mortality in patients with severe sepsis.²⁰ In univariate analysis, the odds ratio for death in the 244 patients who received etomidate compared to those who did not receive etomidate was 1.53 (95% confidence interval, 1.06–2.26). However, the association between etomidate exposure and outcome was lost in multivariate analysis, with a CI that included 1 (OR, 1.82; 95% CI, 0.52–6.36). In addition, the study had serious methodologic issues that make interpretation difficult. First, whether all "etomidate" patients received just a single dose for RSI is uncertain — an important distinction because the effect of etomidate on the adrenal system is both dose-dependent and cumulative. Second, severity of patient illness (i.e., extent and severity of hypotension) likely played a role in the selection of etomidate as the

induction agent. The potential effect of illness severity was underscored by the study's findings that vasopressor use increased the risk for death 38-fold in univariate analysis and 106-fold in multivariate analysis.

Other studies reported varying and contradictory results on etomidate exposure and clinical outcome. Another retrospective evaluation of a prospectively collected database of 159 septic shock patients demonstrated no difference in outcomes when etomidate was used. In fact, patients who received etomidate were less likely to require cardiovascular interventions than were those who received other agents.²⁶ A study by Riché et al. evaluated the relation between response to corticotropin-stimulation testing and mortality in patients with septic shock of abdominal origin and found no outcome differences between patients who did and did not receive etomidate.²⁷ In addition, preliminary results of a study involving 224 septic shock patients and of a second trial involving 90 trauma patients also demonstrated no increase in mortality when induction doses of etomidate were used during RSI.^{21,22}

OUR COMMENTS ON PREVIOUS AND CURRENT ASSERTIONS AND OUR RECOMMENDATIONS FOR CLINICIANS

Pending the results of a proposed prospective study, clinicians are left with the question of how to apply conflicting data to current practice.^{7,8} A number of different assertions about the use of etomidate in septic shock have been made, but what is the practicing clinician to do?^{1,2,3,4,5,6,7,8,15,20,21}

Prior Assertion: Use of etomidate for intubation should be considered contraindicated in patients with septic shock.

Comment: Etomidate has hemodynamic stability that is superior to that of all other induction agents, with the possible exception of ketamine. The implications of choosing another induction agent that has significant hypotensive potential are considerable. Hypotension during acute illness, even when transient, increases mortality by two- to threefold.^{28,29,30} Sepsis patients may be especially prone to postintubation hypotension, with a reported 60% of patients requiring vasoactive support after intubation.²⁹ Based on current data, no convincing evidence exists to warrant abandonment of etomidate for septic shock patients, and no data clarify whether substitution of an alternative agent might increase, decrease, or have no effect on mortality or other, more refined, outcome definitions.

Prior Assertion: Ketamine should be used to intubate septic shock patients, unless there are contraindications or it is not available.

Comment: Ketamine also has an excellent hemodynamic profile and might be a reasonable alternative to etomidate. However, ketamine is not available in many EDs and ICUs, and physicians might be less familiar with its use. In addition, the possible effects of ketamine in sepsis have not been studied. Also unclear is how ketamine's known adverse effects, such as emergence reactions, might affect the incidence of ICU delirium and its associated morbidity and

mortality.³¹ Although studies might determine that ketamine is a reasonable alternative agent to etomidate for intubation of hypotensive patients with sepsis, no evidence currently exists to support this contention. However, if the clinical option is between ketamine and an agent known to induce or worsen existing hypotension, ketamine would be the reasonable choice.

Prior Assertion: If etomidate is used, empirical supplemental corticosteroids are required to offset any potential mortality effect.

Comment: There is no evidence to support this approach, and we do not recommend it.

Prior Assertion: If etomidate is used, physicians providing subsequent care should be advised so that they can take this into account when interpreting adrenal function testing.

Comment: This assertion is difficult to argue against. Advising the admitting physician that a patient has received etomidate is important because of the drug's potential to affect the results of adrenal testing, should it be undertaken, although new guidelines deemphasize the use of adrenal testing in septic shock patients. Recent studies suggest that neither corticosteroid administration nor adrenal testing is useful in treating patients with septic shock, seriously calling into question any connection among etomidate, adrenal function, and outcome.^{32,33}

SUMMARY

In summary, for septic shock patients who present acutely, the mainstay of treatment is resuscitation to correct end-organ perfusion deficit and oxygen debt. The first consideration for patients with significant resuscitation requirements is the airway. Etomidate and ketamine are the two induction agents known to have the least potential to induce or worsen hypotension. When faced with a septic shock patient who requires emergency intubation, we recommend administration of an induction agent with pharmacologic properties that minimize the likelihood of worsening hypotension and of further compromising tissue perfusion. Pending the results of prospective trials, we recommend that clinicians choose etomidate for induction. No convincing evidence supports the assertion that etomidate should be avoided in patients with septic shock. If etomidate is not available or if the clinician is more familiar with ketamine as an induction agent, ketamine is an acceptable alternative.

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1. Schneider RE and Caro DA. Sedative and induction agents. In: Walls RM et al (eds): Manual of Emergency Airway Management, 2nd ed. *Philadelphia: Lippincott Williams & Wilkins* , 2004:189.
2. Zed PJ et al. Etomidate for rapid sequence intubation in the emergency department: Is adrenal suppression a concern? *CJEM* 2006 Sep; 8:347.
3. Zuckerbraun NS et al. Use of etomidate as an induction agent for rapid sequence intubation in a pediatric emergency department. *Acad Emerg Med* 2006 Jun; 13:602.
4. Murray H and Marik PE. Etomidate for endotracheal intubation in sepsis: Acknowledging the good while accepting the bad. *Chest* 2005 Mar; 127:707.
5. Jackson WL Jr. Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock? A critical appraisal. *Chest* 2005 Mar; 127:1031.
6. Annane D. ICU physicians should abandon the use of etomidate! *Intensive Care Med* 2005 Mar; 31:325.
7. Shirley PJ and McAuley DF. Etomidate — Misused or misunderstood? *Anaesthesia* 2006 Feb; 61:190.
8. Morris C and McAllister C. A reply to: Etomidate — Misused or misunderstood? *Anaesthesia* 2006 Feb; 61:191.
9. Lundy JB et al. Acute adrenal insufficiency after a single dose of etomidate. *J Intensive Care Med* 2007 Mar/Apr; 22:111.
10. Evans RH and Hill RG. The GABA-mimetic action of etomidate [proceedings]. *Br J Pharmacol* 1977 Nov; 61:484P.
11. Sakles JC et al. Airway management in the emergency department: A one-year study of 610 tracheal intubations. *Ann Emerg Med* 1998 Mar; 31:325.
12. Yeung JK and Zed PJ. A review of etomidate for rapid sequence intubation in the emergency department. *CJEM* 2002 May; 4:194.
13. Ebert TJ et al. Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. *Anesthesiology* 1992 May; 76:725.
14. Gooding JM et al. Cardiovascular and pulmonary responses following etomidate induction of anesthesia in patients with demonstrated cardiac disease. *Anesth Analg* 1979 Jan/Feb; 58:40.

15. Oglesby AJ. Should etomidate be the induction agent of choice for rapid sequence intubation in the emergency department? *Emerg Med J* 2004 Nov; 21:655.
16. Modica PA and Tempelhoff R. Intracranial pressure during induction of anaesthesia and tracheal intubation with etomidate-induced EEG burst suppression. *Can J Anaesth* 1992 Mar; 39:236.
17. Watt I and Ledingham IM. Mortality amongst multiple trauma patients admitted to an intensive therapy unit. *Anaesthesia* 1984 Oct; 39:973.
18. Wagner RL et al. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. *N Engl J Med* 1984 May 31; 310:1415.
19. Morris C and McAllister C. Etomidate for emergency anaesthesia; mad, bad and dangerous to know? *Anaesthesia* 2005 Aug; 60:737.
20. Lipiner-Friedman D et al. Adrenal function in sepsis: The retrospective Corticus cohort study. *Crit Care Med* 2007 Apr; 35:1012.
21. Dmello D et al. ICU physicians should not abandon the use of etomidate! *Crit Care Med* 2006; 34:A110.
22. Turk BF et al. Does etomidate confound the diagnosis of adrenal insufficiency in the trauma patient? *Crit Care Med* 2005 Dec; 33:A74.
23. Schenarts CL et al. Adrenocortical dysfunction following etomidate induction in emergency department patients. *Acad Emerg Med* 2001 Jan; 8:1.
24. Absalom A et al. Adrenocortical function in critically ill patients 24 h after a single dose of etomidate. *Anaesthesia* 1999 Sep; 54:861.
25. Annane D et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002 Aug 21; 288:862.
26. Ray DC and McKeown DW. Effect of induction agent on vasopressor and steroid use, and outcome in patients with septic shock. *Crit Care* 2007 May 16; 11:R56.
27. Riché FC et al. Adrenal response in patients with septic shock of abdominal origin: Relationship to survival. *Intensive Care Med* 2007 Oct; 33:1761.
28. Jones AE et al. Emergency department hypotension predicts sudden unexpected in-hospital mortality: A prospective cohort study. *Chest* 2006 Oct; 130:941.
29. Mort TC. Complications of emergency tracheal intubation: Hemodynamic alterations — Part I. *J Intensive Care Med* 2007 May/Jun; 22:157.

30. Franklin C et al. Life-threatening hypotension associated with emergency intubation and the initiation of mechanical ventilation. *Am J Emerg Med* 1994 Jul; 12:425.

31. Ouimet S et al. Subsyndromal delirium in the ICU: Evidence for a disease spectrum. *Intensive Care Med* 2007 Jun; 33:1007.

32. Dellinger RP et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008 Jan; 34:17.

33. Sprung CL et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008 Jan 10; 358:111.

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