

CONTROVERSIES

Etomidate for rapid sequence intubation in the emergency department: Is adrenal suppression a concern?

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Introduction

Etomidate has become one of the most commonly used induction agents in the United States during emergency department (ED) endotracheal intubation.¹⁻³ While etomidate may be popular, concerns have been raised about possible adrenal suppression and subsequent adverse effects.⁴⁻⁷ In this paper we critically evaluate the recent literature and perspectives regarding the effect of etomidate on the adrenocortical system.

Background

Rapid sequence intubation (RSI) has become the standard technique for airway management in the ED.^{8,9} Administration of an induction agent followed by a rapidly acting neuromuscular blocking agent to produce unconsciousness and motor paralysis provides optimal intubating conditions while minimizing the risk of aspiration in unprepared patients.^{9,10}

The induction agents currently used for RSI in North

America include the barbiturate thiopental, the benzodiazepine midazolam and miscellaneous agents such as ketamine and propofol. Etomidate is a sedative-hypnotic introduced into clinical practice in Europe in 1972. It is chemically distinct from other commonly used induction agents,¹⁰⁻¹² and was initially used for the maintenance of sedation in the operating room and intensive care unit (ICU).¹³ Etomidate has a rapid onset and recovery, minimal cardiovascular effects, respiratory depression or histamine release, and provides protection from myocardial and cerebral ischemia. Given these traits, etomidate has been touted as the ideal induction agent for select ED patients requiring RSI intubation. It has recently gained popularity in many Canadian EDs.^{1,11,14}

Adrenal suppression from etomidate infusion in the intensive care unit

In 1983, the year the etomidate was approved for use in the US, a trend toward increased mortality was reported in critically ill patients receiving continuous infusion etomidate.¹⁵ An increase in mortality was subsequently con-

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firmed in a larger series of trauma patients and was found to be due to etomidate-induced inhibition of adrenocortical function.¹⁶

Etomidate inhibits the conversion of cholesterol to cortisol by a reversible and concentration-dependent blockade of 11β -hydroxylase and, to a lesser extent, 17α -hydroxylase.^{17,18} Adrenal suppression resulting in decreased cortisol and aldosterone levels has been documented to occur approximately 30 minutes after a single induction dose of etomidate and can last for up to 24 hours.^{19–22} This adverse effect has been found to be clinically significant during continuous etomidate infusion when administered for days to weeks.^{15,16} Etomidate infusions are no longer used for sedation in critically ill patients; however, etomidate continues to be used for induction of RSI as a single-bolus dose in the ED setting.^{1–3}

Adrenal suppression from etomidate for rapid sequence intubation in the emergency department

The effect of etomidate on adrenocortical function and the relative safety of a single-bolus dose of this agent during RSI has recently received attention.^{4–7} Two published papers have called for the immediate discontinuation of etomidate for RSI;^{6,7} while others have proposed alternative solutions.^{4,5}

The adrenocortical effects of etomidate after a single bolus for induction have been studied in a number of settings.⁵ Several small trials have evaluated patients receiving etomidate for elective surgery induction and have demonstrated significant but transient (<24 h post-administration) adrenocortical suppression. It is uncertain if this transient adrenal insufficiency results in significant clinical manifestations, as it is still poorly studied. Moreover, study patients to date have generally been healthy with a low risk of mortality, and the methods for evaluating adrenocortical function were not standardized.

Evidence demonstrating transient adrenocortical suppression has also been documented in critically ill patients requiring intubation preoperatively, or in the ED. It has been hypothesized that such patients, particularly those with septic shock, are more likely to experience poor outcomes if any transient but clinically significant adrenal insufficiency occurs. To date only 1 trial involving 31 patients has formally evaluated adrenal function following etomidate administration in the ED.²² Subjects in this study were randomized to induction with either etomidate or midazolam, and subsequent neuromuscular blockade with succinylcholine. Adrenocortical function was assessed at 4, 12 and 24 hours post-induction using a cosyntropin stimulation test (CST). The results indicated that despite a sig-

nificantly abnormal CST in the etomidate group at 4 hours, all patients in both groups had a normal CST at 12 hours. Serum cortisol levels for all patients remained within the normal range throughout the study period.

Patients with known or suspected septic shock are of particular interest, and at the heart of the etomidate controversy.^{4–7} Patients with sepsis frequently require vasopressor support. Due to the low potential of etomidate to cause hemodynamic instability, it is an attractive induction agent for such patients.^{1,2} However, etomidate-induced adrenal insufficiency could worsen clinical outcomes in septic shock patients who are already at increased risk for relative adrenal insufficiency.²³ The controversy has resulted in significant debate in the literature on induction agents for this particular patient population.^{4–7} Although it is conceivable that other subgroups of patients undergoing intubation in the ED are at similar risk, hence the calls by some authors to discontinue etomidate use altogether,^{6,7} most of the current debate has focused on the patients with septic shock.

Options proposed for septic shock patients

Three approaches have been proposed for the use of etomidate in septic shock patients: 1) eliminate etomidate use altogether in this subgroup; 2) use a lower dose of etomidate in conjunction with lower doses of other induction agents; and 3) routinely administer concomitant corticosteroids with etomidate.⁵

If etomidate is not used in septic shock patients, an alternative agent must be considered. The selection of an induction agent in a hypotensive patient is often a difficult decision that involves weighing intubating conditions against potential adverse effects. Midazolam is often under-dosed as an induction agent and its onset is often unpredictable.²⁴ Propofol and thiopental have rapid and predictable responses, but may induce further hypotension. Ketamine is probably the best alternative to etomidate given its stable hemodynamic effects.

The use of a lower dose of etomidate in combination with lower doses of other induction agents has inherent appeal. Unfortunately, however, even low doses of etomidate (as little as 0.04 mg/kg, or approximately 1/5th to 1/10th the standard induction dose) have been demonstrated to cause adrenal suppression.²⁵ In addition, intubating conditions have not been evaluated using this approach, and it is conceivable that reducing the dose may compromise the intubating conditions compared with a standard 0.2–0.3 mg/kg dose.^{1,2}

The suggestion to administer routine corticosteroid supplementation in patients with suspected septic shock receiving etomidate is complex and requires some back-

ground. In 2002, a landmark study by Annane and colleagues evaluated the role of corticosteroids to reduce 28-day mortality in a subgroup of patients with early septic shock who were non-responders (NR) to a standard 250- μ g CST.²⁶ Patients in this subgroup who received hydrocortisone 50 mg IV every 6 hours plus fludrocortisone 50 μ g orally daily for 7 days had a significant reduction in time to vasopressor withdrawal and 28-day mortality. Of note, 21 months into the trial, the investigators amended their protocol to exclude patients who received etomidate for induction of RSI because 94% of patients who had received etomidate for RSI were NR, undermining the ability of the trial to determine the general incidence and severity of relative adrenal insufficiency in early septic shock. The mortality rate in the NR subgroup who received etomidate was 54.8% in patients who received corticosteroids supplementation and 75.7% in patients who did not ($p = 0.0315$). In the entire NR subgroup, the mortality rate was 53.0% in patients who received corticosteroids and 63.0% in patients who did not.

The data from the Annane trial suggests that in early septic shock the use of etomidate for induction of RSI is associated with high rates of relative adrenal insufficiency. More importantly, it is unclear whether clinical outcomes are worse in the NR patients who receive supplemental corticosteroids and etomidate compared with those who do not receive etomidate. It has been argued that although the induction of short-term adrenal insufficiency may lead to increased mortality associated with the use of etomidate in early septic shock, the use of corticosteroids in NR patients may offset this risk.⁴ The Annane trial supports this hypothesis, as the mortality rate in the NR patients who received etomidate RSI and corticosteroids (54.8%) was virtually identical to the mortality rate in the entire cohort of NR patients who received corticosteroids (53.0%).

Providing routine empiric corticosteroid supplementation due to the potential induction of short-term adrenal suppression in septic shock patients who receive etomidate for RSI is controversial. Irrespective of baseline adrenal testing, studies in early and late septic shock have shown that low-dose corticosteroids reduce the duration of vasopressor requirements and should be considered for use in patients who remain hypotensive despite adequate fluid, vasopressor and oxygen delivery strategies, or in patients who are not tolerating vasopressor agents.²⁷ Although the Annane trial demonstrates a mortality benefit from low-dose corticosteroids in patients with early septic shock (0–8 h) who are NR to a 250- μ g CST, this mortality benefit did not extend to all patients in the trial, and smaller trials of low-dose corticosteroid treatment in patients with septic

shock for longer time periods have not shown the same mortality benefit.²⁷ Two subsequent meta-analyses suggest that low doses of corticosteroids may reduce mortality from septic shock; however, these analyses have inherent limitations associated with the pooling of clinically heterogeneous data from small randomized controlled trials, and should be viewed as hypothesis-generating data.^{28,29} Thus it remains unclear if routine use of supplemental corticosteroids in all septic shock patients, irrespective of adrenal function, confers a mortality benefit with an acceptable adverse effect profile. It is hoped that the recently completed Corticus trial will shed further light on this topic.³⁰ Therefore, it is also unknown if routine corticosteroid supplementation is beneficial in septic shock patients undergoing RSI with etomidate.

Summary

There is significant evidence demonstrating that etomidate, when used as an induction agent to facilitate RSI, causes transient adrenal insufficiency of uncertain clinical effect. As many patients undergoing intubation in the ED are under physiologic stress, this effect could be of concern, particularly for the subgroup of patients with septic shock. However, the clinical relevance in patients receiving this agent for induction of RSI in the ED is uncertain. To date, morbidity and mortality data associated with surrogate outcomes involving the measurement of adrenal activity are limited, and further research is necessary. In the absence of a consensus regarding the clinical significance of transient adrenal insufficiency, we believe a prudent approach is to avoid the use of etomidate in patients with known or suspected septic shock or any other patients who may be harmed by transient adrenal suppression. However, if etomidate is administered to patients with septic shock, we suggest a baseline serum cortisol and a 250- μ g CST test. Until the CST results are available, patients should be treated with hydrocortisone 50 mg IV every 6 hours. Patients who have an incremental cortisol response of <250 nmol/L after the 250- μ g CST should receive hydrocortisone 50 mg IV every 6 hours \pm fludrocortisone 50 μ g orally, daily for 7 days.²⁶

Competing interests: None declared.

Key words: etomidate; intubation; adrenal insufficiency

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