Clinical Controversies: Etomidate as an Induction Agent for Endotracheal Intubation in Patients With Sepsis

Opposing authors provide succinct, authoritative discussions of controversial issues in emergency medicine. Authors are provided the opportunity to review and comment on opposing presentations. Each topic is accompanied by an Editor’s Note that summarizes important concepts. Participation as an authoritative discussant is by invitation only, but suggestions for topics and potential authors can be submitted to the section editors.

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Editor’s note: Because it exhibits many favorable characteristics, including rapid onset, minimal respiratory depression, and preservation of hemodynamic stability, etomidate has frequently been used as an induction agent for endotracheal intubation of septic patients. This practice has recently been questioned in light of studies demonstrating that even a single dose of etomidate may interfere with cortisol production and produce relative adrenal insufficiency in critically ill patients. In this installment of Clinical Controversies, pro and con advocates present opposing perspectives and discuss the available evidence and arguments that must be considered in deciding to embrace or abandon the use of etomidate as an induction agent for endotracheal intubation of septic patients.

CONTINUE TO USE ETOMIDATE FOR INTUBATION OF PATIENTS WITH SEPTIC SHOCK

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Etomidate, long considered safe and reliable for emergency intubation, has recently come under fire. Despite the lack of a single prospective, randomized study scientifically demonstrating any adverse patient outcome related to etomidate’s transient inhibition of 11β-hydroxylase, the enzyme involved in the final step of cortisol production, some authors have called for a ban of the use of etomidate in sepsis, using such hyperbolic terminology as “pharmacologic adrenalectomy.” What does the evidence really show?

Critically ill patients have a high incidence of attenuated response to exogenous cosyntropin, although the meaning of this observation is not known. Etomidate appears to transiently increase the likelihood that a patient will exhibit this phenomenon. Absalom randomized 35 critically ill patients undergoing general anesthesia to induction with etomidate or thiopental. No cortisol level was below the normal range, but significantly more patients in the etomidate group had reduced response to cosyntropin. No intervention was performed and there was no difference in outcome. Mohammad et al retrospectively analyzed 152 patients with septic shock who had a cosyntropin stimulation test. There were no differences in serum cortisol levels between the patients who had received etomidate 7 to 10 hours before study enrollment and nonetomidate patients, but 76% of etomidate versus 51% of nonetomidate patients had “relative adrenal insufficiency,” as defined by the authors. From these and other studies, it is reasonable to conclude that a single dose of etomidate increases the likelihood that a patient with sepsis will have a reduced response to exogenous cosyntropin. Cortisol levels may similarly be reduced, but not below the normal range.

Although no prospective, randomized study has shown an increase in mortality related to a single use of etomidate in patients with sepsis, several authors have used retrospective analyses to improperly claim that etomidate increases mortality. den Brinker et al retrospectively analyzed children with meningococcal sepsis or shock and found that etomidate was among those factors predictive for a decrease in 11β-hydroxylase activity. Although they rightly acknowledge that the study was not designed to determine the effect of etomidate on adrenal function or mortality, and no mortality effect was actually observed, the authors nevertheless speculate that etomidate “might have” increased the risk for mortality. Lipiner-Friedman et al retrospectively analyzed data from the Cortisus sepsis study and reported that for patients who received etomidate, nonsurvivors had both lower cortisol levels and less response to exogenous cosyntropin than survivors. The authors paid scant attention to...
the fact that the actual cortisol differences between nonsurvivors and survivors in the etomidate group were small, that all cortisol levels were in the normal range, and that the reduction in cosyntropin response in the etomidate patient groups was less than that observed for nonetomidate patients. Although their own 95% confidence interval argues to the contrary, the authors inexplicably assert that etomidate is associated with an increased risk of death.

Studies conducted specifically to compare mortality in etomidate versus nonetomidate patients have failed to demonstrate any difference. Mohammad et al. found no difference in mortality rates for shock patients receiving etomidate versus those who did not. Ray and McKeown found no increases in vasopressor use or mortality for septic shock patients receiving etomidate. Riché et al. found no link between cosyntropin response and mortality and no difference in mortality between etomidate and nonetomidate patients with intra-abdominal sepsis. Sprung et al. and the Corticus study group confirmed an association between etomidate and the likelihood of reduced adrenal response to cosyntropin. They appropriately avoided drawing any unsupported conclusions about the higher observed mortality in their (nonrandomized) etomidate patients.

Hypotension occurring at any time is associated with increased mortality in critically ill patients. Etomidate’s hemodynamic profile is superior to that of virtually all available induction agents. In patients with limited cardiovascular reserve, intubation and mechanical ventilation are often associated with hypotension, regardless of the induction agent used. Compounding this effect by using an agent that is known to decrease mean arterial blood pressure seems unnecessarily risky. Ketamine, which some consider a reasonable alternative to etomidate, is not available in many emergency departments or critical care units, is not well studied for this use, and is itself associated with adverse effects.

According to the supporting evidence, including that cited above, calls for a ban on etomidate for intubation in sepsis are not justified. Finfer states, “Perhaps the greatest service we can do our patients is to conduct the large, high-quality trials needed to base our clinical practice on truly robust evidence.” Etomidate opponents should advocate such a properly designed, randomized trial, lest they cause further harm by forcing those of us charged with resuscitation of these vulnerable patients to use agents much more likely to disturb their fragile hemodynamic balance, with potentially fatal consequences.

**Funding and support:** By Annals policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest. The authors have stated that no such relationships exist. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement.

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doi:10.1016/j.annemergmed.2008.01.344

**REFERENCES**


**ETOMIDATE: NOT WORTH THE RISK IN SEPTIC PATIENTS**

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A 3-year-old boy presents to the emergency department (ED) with a 1-day history of fever, a coalescing petechial rash, and a blood pressure of 40 mm Hg. A 75-year-old febrile nursing home patient has a pulse rate of 120 beats/min, blood pressure of 80 mm Hg, and a grossly infected urinary catheter. The child is lethargic and fatigued, whereas the nursing home patient has agonal respirations. Both of these patients are obviously septic, both have a 50% chance of having adrenal insufficiency, and in North America, both will almost certainly undergo rapid sequence intubation with etomidate. After the intubation, both patients will have a more than 70% chance of adrenal insufficiency.

Two facts and a great deal of opinion go into questioning the wisdom of using etomidate in these patients. The first fact in this debate is that sepsis produces adrenal insufficiency. The second and equally well-proven fact is...