

Critical Care Therapeutics

The Uncertain Risk of Single-Dose Etomidate in the Critically Ill

Gilles L. Fraser, PharmD, FCCM* and Richard R. Riker, MD, FCCP†

This feature examines the impact of pharmacologic interventions on the treatment of the critically ill patient — an area of health care that has become increasingly complex. Recent advances in drug therapy for adult ICU patients (including evolving and controversial data) will be reviewed and assessed in terms of clinical, humanistic, and economic outcomes. Direct questions or comments to Gil Fraser, PharmD, at fraseg@mmc.org.

A year and a half ago, we reviewed the importance of adrenal function in the critically ill and questioned the relevance of single-dose, etomidate-induced interference with cortisol production.¹ Since that time, the issue has received significant attention with two analyses and two editorials in major medical journals.²⁻⁵ This discussion will focus on the controversy surrounding the use of etomidate to facilitate intubation in critically ill patients.

BRIEF OVERVIEW OF ADRENAL INSUFFICIENCY IN THE CRITICALLY ILL

The stress of critical illness activates the hypothalamic-pituitary-adrenal axis resulting in the release of cortisol from the adrenal cortex. Steroid release is essential because it 1) increases blood glucose to supply energy and substrate for cellular function and repair; 2) is required for the vasoconstrictive function of angiotensin II, epinephrine, and norepinephrine; and 3)

offers anti-inflammatory activity inhibiting cytokine production and migration of circulating inflammatory cell migration into tissues.⁶ The description of adequate adrenal function in the stressed patient is quite controversial with some suggesting that it is represented by a baseline cortisol level of greater than 20 to 25 mcg/dL; while others believe it is characterized by an increase of baseline cortisol of more than 9 mcg/dL following corticotropin administration.¹ Depending on the population studied and the diagnostic criteria used, adrenal insufficiency is noted in 30% to 76% of ICU patients. What is not in contention is that blunted adrenal responsiveness has a negative impact on patient outcomes if left untreated.⁷

ETOMIDATE PHARMACOLOGY

Etomidate is considered by many to be the induction agent of choice to facilitate rapid-sequence intubation.⁸ This nonbarbiturate, nonbenzodiazepine sedative seems ideal for this indication: it has a

predictable rapid onset (15 sec), an offset (3 to 7 min) of action, and is hemodynamically neutral.⁵ Side effects include pain on injection, nausea and vomiting, and myoclonic movements. The latter can be limited with concurrent use of midazolam.⁹ Caution is advised when using this agent in patients with seizures, and published pediatric experience is not extensive.¹⁰ Importantly, etomidate can suppress adrenal function through reversible inhibition of 11 beta-hydroxylase, an enzyme involved in the final step of endogenous cortisol production.

ETOMIDATE RISKS

Favorable pharmacologic features tempted some to use etomidate as a continuous infusion for ICU sedation in the early 1980s. Clinicians from a Scottish trauma ICU reported an increase in mortality from 25% to 44% (before vs after initiation of etomidate sedation) despite similar patient acuity.¹¹ Investigators subsequently determined that the increased mortality was likely related to etomidate-induced adrenal insufficiency via inhibition of cortisol production, and as a result, long-term etomidate use fell out of favor.^{12,13}

Whether the benefits of single-dose etomidate outweigh the risks remains unclear. The impact of short-term etomidate on cortisol production is known.^{4,14} It appears that the duration of drug-induced interference with adrenal function is less than 24 hours for most

*†Department of Medicine, Maine Medical Center, Portland, ME 04102. Address correspondence to Gil Fraser, PharmD, Maine Medical Center, 22 Bramhall Street, Portland, ME 04102; E-mail: fraseg@mmc.org.

patients given a single dose, and this is generally thought to be clinically insignificant.¹⁵ Unfortunately, these data were not derived from critically ill patients, a population that may be at increased risk for the detrimental effects of adrenal insufficiency. Studies in more seriously ill patients suggest that the duration of adrenal insufficiency may be sustained for at least 24 hours and perhaps even longer.^{3,15} The importance of these findings is only beginning to be appreciated.

ETOMIDATE ICU DATA

The incidence of adrenal insufficiency in septic shock approaches 77% and is associated with increased mortality if exogenous corticosteroids are not administered.¹⁶ Blunted adrenal responsiveness in septic shock is clearly confounded by etomidate use, as it occurs in up to 94% of septic patients receiving this drug.¹⁷ Twenty-eight day crude mortality is significantly higher if these patients are not treated with corticosteroids (75.7% vs 54.8%, $P = 0.03$). Per personal communication with D. Annane, steroid replacement appears to eliminate this negative effect, with similar mortality without regard to the adrenal unresponsiveness associated with etomidate use. Thus, it appears that provision of corticosteroids may be protective for septic shock patients with adrenal insufficiency associated with etomidate.⁵ Some would argue however, that this feature of etomidate almost always necessitates the use of corticosteroids, and that we should not compound an iatrogenic event (etomidate-induced adrenal insufficiency) with other iatrogenic events (corticosteroid-induced hyperglycemia, immunosuppression, neuromuscular weakness,

and impaired wound healing). Although not proven clinically, a potential acute consequence of corticosteroid use impacting patient outcomes includes loss of tight glucose control, an issue recently highlighted in a consensus statement on managing sepsis.¹⁸ More long-term effects such as impaired functional capability in survivors of acute respiratory distress syndrome is profoundly influenced by systemic corticosteroid administration for as long as 3 months after ICU discharge.¹⁹

Other data from 62 ICU patients who were mechanically ventilated for at least 1 day implicate single-dose etomidate as a major risk factor for the development of adrenal insufficiency in patients with or without sepsis.³ Forty-three percent of all study patients had adrenal insufficiency when assessed 24 hours after endotracheal intubation. The only variable remaining in a multivariate analysis as an independent risk factor for the development of impaired adrenal function was single-bolus etomidate (OR 12.21; 95% CI 2.99 to 49.74). Interestingly, the diagnosis of severe sepsis was not identified as a risk factor for adrenal insufficiency. Mortality was higher in those with adrenal insufficiency (70.4% vs 31.4%, $P < 0.005$), yet corticosteroids were administered in only one-third of these patients. This study highlights the risks of etomidate and suggests that adrenal insufficiency in the critically ill is commonly undetected and untreated.

ALTERNATIVES TO ETOMIDATE?

Assessing the morbidity of any given drug regimen must include the potential risks associated with alternative strategies. The choice of medications for intubation in patients with sepsis is complicated

by the need for a predictable response that avoids hemodynamic instability. Indeed, two-thirds of deaths occurring during induction are due to cardiovascular events.²⁰ Succinylcholine, midazolam, fentanyl, and propofol have been used to facilitate intubation, but each has its own limitations and carry its own unique risks.⁸

WHAT MORE DO WE NEED TO KNOW?

- It appears that nearly all vasopressor-dependent septic patients who receive etomidate will develop adrenal insufficiency as currently defined. The value of routinely adding corticosteroids compared with awaiting the results of adrenal evaluation in these patients needs to be evaluated. At the very least, all patients with septic shock who received etomidate should be tested for adrenal unresponsiveness given the 94% incidence reported.
- It is known that untreated adrenal insufficiency in the ICU is associated with increased mortality, but the effect of etomidate interference with adrenal function remains in the early stages of understanding.³ Since etomidate is especially useful in hemodynamically unstable patients (who are generally sicker than others), observational results may be biased, and randomized comparative trials will be required to evaluate drug-induced morbidity.
- It appears that the duration of single-dose, etomidate-induced, adrenal suppression is longer in critically ill patients than in those with elective surgical procedures. The mechanism for this is not clear. Critically ill, stressed patients require consistent production of cortisol to

maintain homeostasis. It is possible, therefore, that the time to recover from diminished production may be longer for these patients than in those who are not stressed.² Serial evaluations of adrenal function need to be performed in this population to help characterize the potential for a sustained etomidate mediated effect on cortisol production.

SUMMARY

Adrenal insufficiency occurs in more than 90% of patients with septic shock that are treated with etomidate, and it is associated with increased risk for death which can be offset by administration of corticosteroids. Until data are available to guide clinicians, the most conservative approach would be to avoid etomidate in patients with sepsis, accepting the less predictable response to other agents for intubation and the greater degree of hypotension associated with their use. Another approach would be to continue to use etomidate but to routinely assess adrenal function with steroid replacement while awaiting test results.

REFERENCES

1. Fraser GL, Yahwak JA, Riker RR. Corticosteroids in the critically ill. *Hosp Pharm.* 2004;32:116-118.
2. Annane D. ICU physicians should abandon the use of etomidate! *Intensive Care Med.* 2005;31:325-326.
3. Malerba G, Romano-Gerard F, Cravoisy A, et al. Risk factors of relative adrenocortical deficiency in intensive care patients needing mechanical ventilation. *Intensive Care Med.* 2005;31:388-392.
4. Jackson WL Jr. Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock? *Chest.* 2005;127:1031-1038.
5. Murray H, Marik PE. Etomidate for endotracheal intubation in sepsis. *Chest.* 2005;127:707-709.
6. Luce JM. Physicians should administer low-dose corticosteroids selectively to septic patients until an ongoing trial is completed. *Ann Intern Med.* 2004;141:70-72.
7. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ.* 2004;329:480.
8. Reynolds SF, Heffner J. Airway management of the critically ill patient. *Chest.* 2005;127:1397-1412.
9. Schwarzkopf KR, Hueter L, Simon M, et al. Midazolam pretreatment reduces etomidate-induced myoclonic movements. *Anaesth Intensive Care.* 2003;31:18-20.
10. Guldner G, Schultz J, Sexton P, et al. Etomidate for rapid-sequence intubation in young children: hemodynamic effects and adverse events. *Acad Emerg Med.* 2003;10:134-139.
11. Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet.* 1983;1:1270.
12. Fellows IW, Bastow MD, Byrne AJ, et al. Adrenocortical suppression in multiply injured patients: a complication of etomidate treatment. *Br Med J. (Clin Res Ed.)* 1983;287:1835-1837.
13. Wagner RL, White PF. Etomidate inhibits adrenocortical function in surgical patients. *Anesthesiology.* 1984;61:647-651.
14. Schenarts CL, Burton JH, Riker RR. Adrenocortical dysfunction following etomidate induction in emergency department patients. *Acad Emerg Med.* 2001;8:1-7.
15. Absalom A, Pledger D, Kong A. Adrenocortical function in critically ill patients 24 h after a single dose of etomidate. *Anaesthesia.* 1999;54:861-867.
16. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA.* 2002;288:862-871.
17. Mokhlesi B. Corticosteroids for patients with septic shock. *JAMA.* 2003;289:43-44.
18. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med.* 2004;32:858-873.
19. Herridge MS, Cheung AM, Tansey CM, et al. One year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med.* 2003;348:683-693.
20. Arbous MS, Grobbee DE, van Kleef JW, et al. Mortality associated with anesthesia: a qualitative analysis to identify risk factors. *Anaesthesia.* 2001;56:1141-1153. ■