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Is It Risky to Give Etomidate to Septic Patients?

Bryan P. White, PharmD | October 28, 2014

Question

Does the reported association of etomidate with increased mortality in septic patients preclude its use for intubation in that population?

Response from Bryan P. White, PharmD

PGY-1 Pharmacy Resident, Albany Medical Center, Albany, New York

Etomidate is a hypnotic agent used for the induction of general anesthesia and is commonly used for rapid sequence intubation (RSI). Medications used in RSI can contribute to hypotension after intubation, which has been shown to be associated with increases in mortality.[1] Although it has been reported that etomidate is associated with hemodynamic stability after administration,[2] there is limited evidence to support this.[3] It is unclear whether the purported superior hemodynamic effect of etomidate may be due to dosing or to a combination of other drugs used for intubation.

Although etomidate may possibly have a safer hemodynamic profile, there is concern that the drug's nonsedative effects, in particular adrenal suppression, may be harmful. The mechanism for adrenal suppression is inhibition of cortisol production. A single dose of etomidate can blunt adrenal function for up to 72 hours through inhibition of ^{11}beta-hydroxylase, which converts ^{11}beta-deoxycortisol to cortisol.[4]

When initially approved, etomidate was also used as a continuous infusion. It is no longer used for longer-term sedation owing to adrenal suppression and possible increased mortality in intensive care unit (ICU) patients.[5] There is concern that adrenal suppression from etomidate, even with short-term use for RSI, may have harmful effects.[6,7]

Adrenal suppression in septic patients is known to be associated with increased mortality, but giving physiologic doses of steroids does not improve outcomes. The landmark CORTICUS study showed no improvement in mortality for adrenally suppressed patients with sepsis who received 50 mg of hydrocortisone every 6 hours vs placebo (39.2% vs 36.1%; *P* = .69). A subgroup analysis revealed a statistically significant increase in mortality in patients who received etomidate for intubation compared with those who did not (45.1% vs 31.5%; *P* = .03).[8] A nonsignificant trend of increased mortality in patients with sepsis who received etomidate was also seen in a subgroup analysis of KETASED,[9] a large randomized trial of intubated critical care patients comparing ketamine with etomidate for intubation.

Because these were subgroup analyses for which the studies were not adequately powered, they are only hypothesis-generating. Newer studies and two meta-analyses are reviewed below.

The available data on etomidate and patient outcomes are varied, with multiple types of studies looking at different endpoints, such as length of stay, vasopressor use, organ failure scores, and mortality. The only prospective trials[10,11] were not powered to evaluate mortality risks associated with etomidate.

Two meta-analyses on the topic have been published. Albert and colleagues[6] reviewed 19 independent data sets and found an increase in mortality among critically ill patients and patients with sepsis that was associated with etomidate use vs other anesthetics. This meta-analysis only included seven trials within the subset of

sepsis; none of these trials was prospective, and none had a primary endpoint of mortality with etomidate vs a comparator in septic patients.

The analysis found many detrimental effects of etomidate in ICU patients, including increased hospital length of stay, increased ICU length of stay, and increased ventilator days.[6] Of note, a prospective, randomized, double-blind clinical trial in patients with suspected sepsis found no difference in length of stay between etomidate and midazolam (7.3 vs 9.5 days, respectively; *P* = .17).[10]

The second meta-analysis examined adrenal suppression and mortality associated with etomidate use in septic patients. Chan and colleagues[7] evaluated 10 trials published between January 1950 and February 2012, five of which were prospective, and found a pooled relative risk of 1.2 for mortality associated with etomidate use. Selected data from the meta-analyses are presented in .

Table 1. Data From the Meta-Analyses of Etomidate

	Number of Trials Evaluating Mortality	Number of Patients With Sepsis	Number of Patients Who Received Etomidate	Mortality in Septic Patients Receiving Etomidate
Albert et al[6]	7	1767	611	Risk Ratio 1.22 (range 1.11-1.35)
Chan et al[7]	5	865	Unavailable	Relative Risk 1.20 (95% CI 1.02-1.42)

CI = confidence interval

Three recent studies not included in the meta-analyses, all retrospective, exemplify the disagreement in the literature. Two trials[12,13] showed no difference in mortality, and one[14] showed a trend toward increased mortality associated with etomidate. These trials are described in more detail in .

Table 2. Retrospective Trials

	Number of Patients With Sepsis	Number of Patients Who Received Etomidate	Number of Centers	Mortality: Etomidate vs Other Agents
Alday et al[12]	166 (propensity-matched cohort)	83	2	45.8% vs 43.4% (*P* = .76)
McPhee et al[13]	2014	1102	Phillips eICU Research Institute Database	37.2% vs 37.8% (*P* = .77)
Sunshine et al[14]	824	452	2	38.7% vs 29.0 % (Adjusted relative risk 1.20, 95% CI, 0.99-1.45)

CI = confidence interval

McPhee and colleagues[13] performed the largest study to date, involving over 2000 patients with sepsis who were intubated with etomidate or other induction agents. The study was powered to find a 7% difference in

mortality. Patients with sepsis were identified using systemic inflammatory response syndrome (SIRS) criteria with a documented source of infection, admission diagnosis of sepsis, or patients with any type of sepsis syndrome listed in the diagnosis/problem list of the medical record.

No difference in hospital mortality was found between etomidate and other induction agents (37.2 % vs 37.8%; *P* = .77). Patients who received etomidate for intubation had lower mean arterial pressures, were older, and received steroids more often, indicating a possible prescribing bias toward etomidate in the sicker patients owing to its favorable effects on hemodynamics.

The currently available data on etomidate used for intubation as a contributor to increased mortality in septic patients are mixed. No adequately powered prospective, randomized, controlled trials have been performed. Two meta-analyses of published data up to 2012 found an increase in mortality,[6,7] whereas recent retrospective studies have not found, or have only demonstrated a trend toward, increased mortality.[11-13] No trial has shown that giving steroids to patients intubated with etomidate improves mortality, suggesting that adrenal suppression may not be the mechanism of the increased mortality.[8,15]

Although no definitive data are available, their totality do present a concerning "safety signal." Clinicians should consider potential mortality risks of etomidate when selecting among drugs for RSI in patients with sepsis. Until more definitive safety data are available, agents other than etomidate should be favored for RSI in patients with sepsis.

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