

## Commentary

# Etomidate, sepsis, and adrenal function: not as bad as we thought?

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See related research by Ray and McKeown, <http://ccforum.com/content/11/3/R56>

## Abstract

The choice of induction agent for endotracheal intubation can have significant downstream effects, especially in critically ill patients. In a retrospective study, Ray and McKeown found that the choice of induction agent had no significant effect on use of vasoactive medications, corticosteroids, or mortality. Given the heated debate regarding corticosteroids in septic shock and the role that etomidate may play in leading to adrenal insufficiency, enthusiasm for etomidate as an induction agent should be tempered by its possible, significant side effects in these critically ill patients.

The period of induction of anesthesia in patients with sepsis continues to carry inherent risk for further compromise in these critically ill individuals. Extreme caution must be exercised in choosing an induction agent to perform endotracheal intubation in these unstable patients. In this issue of *Critical Care*, Ray and McKeown [1] report a retrospective review in which they examine the influence of induction agent on further utilization of vasoactive medications, corticosteroids, and mortality, with a particular focus on etomidate.

Etomidate is known to cause adrenal suppression, both after a single dose and with prolonged infusion [2,3]. The clinical significance of this drug effect continues to be debated, but etomidate does not carry the significant acute hemodynamic effects of other induction agents [4]. This makes it a common choice to facilitate endotracheal intubation in intensive care unit (ICU) patients, particularly those with hypotension or who are at risk for hypotension during airway management. In this retrospective study, the choice of induction agent (etomidate, propofol, thiopental, or 'other' [midazolam, ketamine, or fentanyl]) was not associated with differences in or doses of vasoactive drug, duration of vasoactive drug infusion, or time from administration of induction drug to commencement of vasoactive drug infusion. Use of etomidate resulted in less frequent need for vasopressor administration at the time of

induction. The use of etomidate did not alter the use of corticosteroids or mortality. However, patients who received etomidate and corticosteroids had higher mortality than did those who received etomidate alone. Even though the patients who received etomidate were sicker than those who received other agents, this raises the possibility that the adrenal suppression caused by etomidate is not as reversible as was once thought [5].

Corticosteroids and relative adrenal insufficiency in sepsis continue to provide areas of intense debate for practitioners of critical care. The precise roles played by total cortisol levels, free cortisol levels [6], and the adrenocorticotropic hormone stimulation test in defining relative adrenal insufficiency in sepsis are not well solidified. For example, in the study conducted by Ray and McKeown [1], patients were empirically given corticosteroids for vasopressor-refractory shock and cortisol levels were not measured, and neither were adrenocorticotropic hormone stimulation tests performed. This is in contrast to multiple studies that utilized various definitions of relative adrenal insufficiency to guide the use of corticosteroids [7]. The role of etomidate is an important factor in this debate. In a recent retrospective study associated with the Corticus group [8], etomidate was associated with increased risk for death by univariate analysis (odds ratio 1.53, 95% confidence interval 1.06 to 2.26) but not by multivariate analysis (odds ratio 1.82, 95% confidence interval 0.52 to 6.36). The univariate significance coupled with nonsignificance but wide confidence intervals by multivariate analysis suggests that larger sample sizes may be needed to address this issue definitively. These data, which conflict with the findings reported by Ray and McKeown [1], raise concerns regarding the safe use of etomidate in septic patients as well as its influence on the findings of future trials conducted to elucidate the role of corticosteroids in treating septic shock.

ICU = intensive care unit.

Despite ongoing controversy regarding the clinical importance of etomidate-induced adrenal suppression, this medication does provide significant short-term benefits. Patients with septic shock uniformly have hemodynamic or respiratory compromise, and commonly both. The institution of mechanical ventilation is a necessary therapy in most of these patients and should be performed as safely, and quickly, as possible. The placement of the endotracheal tube should be performed by relatively experienced hands and in a setting (in terms of both location and anesthesia equipment and personnel) that is best for the patient [9]. The use of other induction agents, such as propofol or thiopental, can result in further hemodynamic compromise during the initiation of mechanical ventilation, which is not an insignificant problem in patients who are in shock [10]. The ability of etomidate to cause less hemodynamic instability in the peri-intubation period cannot be ignored. Although the debate regarding the adrenal axis in sepsis continues, the need for respiratory support in patients in shock is rarely questioned. Mechanical ventilation is a necessary supportive therapy for many patients in septic shock, and providing an environment in which the operator can place an endotracheal tube as efficiently as possible with avoidance of further significant hemodynamic or respiratory compromise is not to be underestimated. The use of opiates (for instance, fentanyl), topical local anesthetics only, or no agent can be considered in a subgroup of ICU patients who require endotracheal intubation.

The limitations of the study by Ray and McKeown [1] must be considered. The authors note that one limitation is the retrospective nature of their data analysis. Despite the fact that a reasonably large number of patients was evaluated ( $n = 159$ ), no power calculation was reported in this study, and the possibility of a type II error must be considered. This is especially pertinent given the 'mixed' results of other work, such as the retrospective Corticus study mentioned above [8]. We can thank Drs Ray and McKeown for adding important information to the literature regarding the use of etomidate in the ICU. The conclusion regarding the safety of this drug for use in facilitating endotracheal intubation should be tempered by the recognition that more data are needed.

## Competing interests

The authors declare that they have no competing interests.

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