JPPT

REVIEW ARTICLE

Pro-Con Debate: Etomidate or Ketamine for Rapid Sequence Intubation in Pediatric Patients

Daniel Scherzer, MD,[1] Mark Leder, MD,[1] and Joseph D. Tobias, MD[2]

[1] Division of Emergency Medicine and Department of Pediatrics, Nationwide Children's Hospital and the Ohio State University, Columbus, Ohio, [2] Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, Columbus, Ohio

When caring for critically ill children, airway management remains a primary determinant of the eventual outcome. Airway control with endotracheal intubation is frequently necessary. Rapid sequence intubation (RSI) is generally used in emergency airway management to protect the airway from passive regurgitation of gastric contents. Along with a rapid acting neuromuscular blocking agent, sedation is an essential element of RSI. A significant safety concern regarding sedatives is the risk of hypotension and cardiovascular collapse, especially in critically ill patients or those with pre-existing comorbid conditions. Ketamine and etomidate, both of which provide effective sedation with limited effects on hemodynamic function, have become increasingly popular as induction agents for RSI. However, experience and clinical investigations have raised safety concerns associated with both etomidate and ketamine. Using a pro-con debate style, the following manuscript discusses the use of ketamine versus etomidate in RSI.

INDEX TERMS adrenal suppression, airway management, etomidate, ketamine rapid sequence intubation

J Pediatr Pharmacol Ther 2012;17(2):142–149

INTRODUCTION

When caring for critically ill or injured children, airway management remains the first priority and a key factor in the ultimate outcome. In these scenarios, airway control with endotracheal intubation is frequently necessary. Rapid sequence intubation (RSI) is generally used in emergency airway management to mitigate potential physiologic responses while protecting the airway from passive regurgitation of gastric contents. Along with a rapid acting neuromuscular blocking agent, sedation is an essential element of RSI. When choosing a sedative to facilitate endotracheal intubation during RSI, the ideal agent would be fast acting, have a short duration of effect, and be reliably effective and safe.[1,2] A significant safety concern regarding sedatives is the risk of hypotension and cardiovascular collapse, especially in critically ill patients or those with pre-existing comorbid conditions. These events may be the result of medications used during RSI, the patient's comorbid conditions, or changes in cardiovascular performance due to the shift from spontaneous to positive pressure ventilation. Hemodynamic control is particularly important for patients in shock or those at risk for inadequate cerebral perfusion pressure (CPP). For this reason, ketamine and etomidate, both of which provide effective sedation with limited effects on hemodynamic function, have become increasingly popular as induction agents for RSI. Agents such as thiopental or propofol are generally not appropriate for critically ill patients, given their vasodilatory and negative inotropic effects.[3,4]

However, experience and clinical investigations have raised safety concerns associated with both etomidate and ketamine. Safety concerns with etomidate came to attention after it had already become a favored RSI sedative, while those related to ketamine preceded its use as an RSI sedative. Etomidate has been shown to transiently impair corticosteroid synthesis after both a single induction dose and a maintenance infusion.[5–11] The potential impact on morbidity and mortality from adrenal suppression has brought the use of etomidate in the critical care setting into question.

Although ketamine may now be considered the preferred drug for RSI, significant hemodynamic effects may occur with its administration, and a recent report outlines cardiac arrest temporally associated with the administration of ketamine for RSI.[12] Given the lack of data sufficient to provide level 1 recommendations for one medication over the other, there is ample room for debate.

PRO: KETAMINE FOR RAPID SEQUENCE INTUBATION

Although in specific clinical circumstances ketamine may result in hypotension from cardiovascular depression, the clinical community has recently been presented with several reports which raise the concern that there may be clinical consequences from the adrenal suppression which occurs following the administration of etomidate. This is not a new story but one that has been known since the 1980s. These issues have resulted in a reappraisal of the role of etomidate in RSI.

Etomidate was introduced into clinical practice in 1972 in Europe and later in 1983 in the United States. It rapidly gained popularity because of its benign pattern of hemodynamic effects even in patients with myocardial ischemia, hemorrhagic shock, and increased intracranial pressure. In its early years, etomidate was even referred to as "relatively atoxic" in the title of one peer-reviewed manuscript.[13] These ill-fated words faced serious challenge by the early 1980s.[14] It was well established by 1984 that etomidate blocked 11β-hydroxylase, resulting in a significant decrease in serum cortisol concentration and adrenocorticotropin hormone (ACTH) responsiveness in patients. Subsequently, increased mortality was noted in critically ill adult patients in the intensive care unit (ICU) when prolonged infusions of etomidate were administered for sedation.[15–17] Etomidate's package insert was amended in 1985 to specifically warn against prolonged infusions and emphasize the risks associated with adrenal suppression.[18] This seemed to quiet the literature on the topic for the next 15 years. Clinicians went on using etomidate frequently as a single-bolus dose to induce anesthesia or for sedation during RSI in patients of all ages, especially those with significant comorbid cardiovascular conditions.

In 1999, Absalom et al[19] noted that even a single dose of etomidate was associated with decreased responsiveness to ACTH in critically ill adults, although the authors refrained from drawing conclusions as to the clinical significance of this finding.[19] Concurrent with that study, Annane et al[20] were investigating the effect of steroid therapy on the outcome of septic patients. Applying a standard word search function to their landmark study published in 2002 revealed the word "etomidate" only once: "During recruitment, we refined the eligibility criteria … we excluded patients who received etomidate…." [20] This group had clearly drawn conclusions as to the potential clinical significance of etomidate's effect on adrenal function. In the Corticosteroid Therapy of Septic Shock (CORTICUS) study, 60% of patients who received etomidate were nonresponders to corticotropin (ACTH) compared to 43% of patients who were etomidate-free.[21] *Post hoc* analyses of CORTICUS data revealed an increased 28-day mortality among patients who received etomidate compared to those who did not (43% versus 31%, respectively). Commenting on the *post hoc* analysis of the CORTICUS study, Lipiner-Friedman et al[22] stated, "Treatment with etomidate was associated with an increased risk of dying, particularly in patients who did not receive steroids." Although steroids provided a benefit for patients who received etomidate, it has been suggested that the better course of action would be to avoid the necessity to compensate for one medicine with another.[23] Concurrent with the concerns regarding etomidate use in septic patients, Hildreth et al[24] studied 30 prospectively enrolled adult trauma patients and found that those treated with etomidate had lower cortisol levels, more ventilator days, and longer ICU stays.

Although a direct causal effect between etomidate and poorer outcomes cannot be proven, it does make sense to avoid adrenal suppression in patients whose physiologic stress response is overwhelmed. The question for clinicians is how much weight to ascribe to the immediate benefit of maintaining hemodynamic stability during RSI versus the less concrete and less immediate problem of adrenocortical suppression. It appears that ketamine provides the current alternative. Ketamine fits the profile of an RSI sedative: 1) its onset of action is rapid; 2) its duration of action is brief; 3) it is reliably effective at producing adequate sedation; and 4) it is at least as safe as other induction agents when used in the right context.

Furthermore, it is the only other intravenous sedative that supports hemodynamics. In a prospective study of 469 randomized patients, including sepsis and trauma victims, Jabre et al[25] concluded "that ketamine is a safe and valuable alternative to etomidate for intubation in critically ill [adult] patients." Ketamine is the only dissociative anesthetic currently in use for patient care. It creates a functional dissociation between the cortex and the limbic system. This effect occurs at a threshold dose (usually 1–2 mg/kg intravenous or 3–5 mg/kg intramuscular). Once the threshold is

reached, dissociation occurs abruptly. When ketamine is administered intramuscularly or as a moderately slow intravenous push over 1 to 2 minutes for the purpose of procedural sedation, dissociative anesthesia is achieved in 1 to 2 minutes without suppressing the reticular activating system. The patient experiences sedation, analgesia, and amnesia while maintaining normal respiratory drive and protective airway reflexes. Further dosing does not have an apparent benefit. As ketamine is metabolized and eliminated, redosing (usually 0.5 mg/kg) may be necessary in 15 to 30 minutes to maintain therapeutic concentrations. Ketamine's onset and duration of action and its favorable respiratory and hemodynamic profile have made it a common choice when analgesia and sedation are needed for brief painful procedures.[26] For RSI, the recommended dose is 1 mg/kg by rapid intravenous push. When administered rapidly (<30 seconds), ketamine produces anesthesia, including respiratory depression, while maintaining hemodynamic stability. Ketamine maintains hemodynamic responses by blocking reuptake of catecholamines. In critically ill patients who require emergent airway management, sedation and positive airway pressure ventilation may be associated with reductions in systemic vascular resistance and central venous return. Ketamine's support of hemodynamic responses is beneficial for these patients. Specific concerns about ketamine include increased intracranial pressure (ICP), increased intraocular pressure (IOP), paradoxical myocardial depression, psychodysleptic effects, and accelerated neuronal apoptotic degeneration. Concerns about ICP and IOP are examples of conventional teachings that are supported by their own repetition rather than evidence. Association of ketamine with increased ICP has been called a "medical myth" by Filanovsky et al.[27] Those authors reviewed the original studies. The studies had small numbers of subjects and significant confounding factors. Filanovsky et al[27] concluded that the evidence for adverse ICP effects is weak and not generalizable. There has been more recent evidence demonstrating no harm and even a benefit of using ketamine in the context of traumatic brain injury (TBI). In their prospective trial of 30 children with increased ICP, Bar-Joseph et al[28] found that intravenous bolus doses of ketamine (1–1.5 mg/kg) alleviated ICP while it maintained mean arterial pressure and CPP. For patients with head injuries, any episode of hypoxia or hypotension contributes to secondary injury. Patients with increased ICP need to maintain their mean arterial pressure in order to maintain CPP. Avoiding RSI/anesthetic induction-related hypotension is a more realistic concern than hypothetical problems with increased ICP.

In the 1960s, when ketamine was known as CI-581, associations with statistically significant but clinically insignificant increases in IOP were noted when it was administered intramuscularly in doses of 2 to 8 mg/kg to children undergoing intraocular procedures.[29] More recently, Drayna et al,[30] in a prospective study of 25 children who served as their own controls, found no statistically or clinically significant rise in IOP associated with ketamine.

There is evidence that ketamine exacerbates myocardial depression in catecholamine-depleted patients. In a rat model of septic cardiomyopathy, bolus doses of etomidate demonstrated a negative inotropic effect, while ketamine had a negative chronotropic effect.[31] In a study of atrial tissue from 16 adults undergoing coronary bypass graft surgery, etomidate was not found to inhibit myocardial contractility, and ketamine was shown to have a slightly negative inotropic effect.[32] More recently, Dewhirtst et al[12] anecdotally reported two patients who suffered cardiac arrest within 1 minute of receiving ketamine for RSI. Both patients received 2 mg/kg ketamine and were in intractable decompensated septic shock and respiratory failure at the time of ketamine administration. These patients' physiologic reserves were likely depleted, thus, it is questionable as to whether they were candidates for an RSI technique that included sedation. Most importantly, caution is warranted regarding the use of any sedative induction agent in severely decompensated, rapidly deteriorating patients. Using an attenuated dose, if any, should be considered. The evidence regarding ketamine's support of cardiovascular function is applicable to clinical situations where endogenous catecholamine stores are not likely to be exhausted. Ketamine's action through endogenous catecholamine release is expected to offset its myocardial depressant effect.

Psychodysleptic effects are looked upon negatively when ketamine is used for medicinal purposes as these generally manifest as emergence reactions. In children, the incidence of these reactions is low (approximately 1.4%),[33] and they are readily remedied with one dose of midazolam provided on an as-needed basis.

PRO: ETOMIDATE FOR RAPID SEQUENCE INTUBATION

Etomidate (Amidate; Abbott Pharmaceuticals, Abbott Park, IL) is an intravenous anesthetic agent whose primary effects of sedation and amnesia are mediated through the γ-aminobutyric acid (GABA) inhibitory neurotransmitter system. Unlike other sedative and hypnotic agents, only the *R*(+) enantiomer has clinical effects. Following intrave-

nous administration, loss of consciousness is rapid (15–20 seconds), and, as with propofol and the barbiturates, its duration of action following a single bolus dose is related to redistribution rather than metabolism and clearance. Beneficial effects on the central nervous system include a decrease in cerebral metabolic rate for oxygen ($CMRO_2$), in cerebral blood flow, and in ICP.[34] As a result of decreased $CMRO_2$ and cerebral blood flow, with a negligible effect on myocardial performance, etomidate decreases ICP while it maintains CPP.[35,36] Contrary to a relatively large clinical experience in the adult population, there are limited data regarding the use of etomidate in pediatric-aged patients; however, most clinical experience favors the use of doses ranging from 0.2 to 0.3 mg/kg.[37,38] There are also anecdotal reports demonstrating the safe use of etomidate for anesthetic induction even in patients with depressed myocardial function.[39,40]

As noted above, the most significant concern with etomidate, and the factor that limits its long-term administration in the ICU setting, is its effects on the endogenous production of corticosteroids. Although initial concerns centered around its use as a continuous infusion in the ICU setting, recent recommendations have admonished its use even when used as a single dose in septic patients. Etomidate inhibits the enzyme 11-β hydroxylase, which is necessary for the production of cortisol, aldosterone, and corticosterone. The duration of adrenal suppression produced by a single induction dose of etomidate has varied from study to study.[40,41] Duthie et al[40] demonstrated a decrease in plasma cortisol levels 1 hour after an induction dose of etomidate. However, at 24 hours, no difference was noted between those patients who received etomidate and those who received other induction agents. Other authors have reported a more prolonged suppression of adrenocortical function of up to 24 hours.[19,41] In a cohort of 40 critically ill adult patients, the incidence of adrenal insufficiency, defined as a failure of the serum cortisol level to increase by 9 mcg/dL after a 250-mcg corticotrophin (ACTH) stimulation test, following a single dose of etomidate was 80% at 12 hours, 9% at 48 hours, and 7% at 72 hours.[42] No difference in outcome was reported following etomidate administration, even when there was accompanying adrenal suppression. In fact, other studies have reported that vasopressor therapy was required less frequently and in smaller doses when etomidate was used for endotracheal intubation in patients with septic shock.[43]

The recent concern regarding the use of etomidate in patients with sepsis stems from the CORTICUS trial.[21] Although the trial was intended to evaluate the efficacy of corticosteroid therapy on outcome in adults with septic shock and adrenal insufficiency, *post hoc* analysis revealed that patients who had received etomidate had a significantly higher mortality rate. Of 96 patients who received etomidate, 60.4% were nonresponsive to ACTH, and their mortality rate at 28 days was 42.7%. By comparison, 44.6% of the 403 patients who did not receive etomidate were nonresponsive to corticotrophin, and the 28-day mortality rate was 30.5%. The increased risk of mortality in patients who had received etomidate was not prevented by the exogenous administration of corticosteroids (45% versus 40%, respectively).[44]

Given these data, significant controversy surrounds the continued use of etomidate, especially in patients with presumed sepsis. There remains uncertainty regarding the clinical significance of the adrenal suppression following a single induction dose of etomidate. Some authors have called for the abandonment or at least a re-evaluation of the use of etomidate.[23,45,46] In some institutions, the decision has been made to remove etomidate from the hospital formulary, operating rooms, emergency department, and ICU. Guidelines published by the American College of Critical Care Medicine states "etomidate should not be routinely used when intubating an infant or child with septic shock.[47]" In the case that it is used, recognition of adrenal suppression as a consequence is advocated.[47] The guidelines cite the adult CORTICUS trial and also a study of mortality and adrenal function in 60 children with meningococcal sepsis, 31 of whom required endotracheal intubation.[5] Of the 31 patients who required endotracheal intubation, 23 received etomidate and 8 did not. Patients who received etomidate had significantly lower cortisol levels, higher ACTH levels, and higher 11-deoxycortisol levels. Seven of 23 patients who received etomidate died versus 1 of 8 in the subset of patients who required endotracheal intubation. Although this suggests etomidate poses a risk factor for mortality, the authors acknowledged that it is difficult to identify the relative contributions of disease severity, endotracheal intubation, and etomidate to mortality.

Clinical practice guidelines for the treatment of septic shock in pediatric and neonatal patients from the American College of Critical Care Medicine[48] state that: "Etomidate is popular as an induction agent because it maintains cardiovascular stability through blockade of the vascular K^+ channel; however, even one dose used for intubation is independently associated with increased mortality in both children and adults with septic shock, possibly secondary to inhibition of adrenal corticosteroid biosynthesis. Therefore, it is not recommended for this purpose." [48] Only one member of

the task force supported the use of etomidate in pediatric septic shock, with the caveat that a stress dose of hydrocortisone be administered.[48]

As etomidate has been removed from many areas that deal with airway management of the critically ill patient, it has been replaced by ketamine. Ketamine was introduced into clinical practice in 1970, and its popularity in the arena of procedural sedation, especially for painful invasive procedures, relate to analgesic properties, rapid onset of action (15–30 seconds), and its beneficial effects on cardiac and respiratory functions.

In patients with sepsis or a systemic inflammatory response syndrome, animal data suggest that ketamine may modulate this response and thereby improve outcome.[49–53] There has been some controversy regarding the use of ketamine in patients with head injury or intracranial hypertension, given that early studies suggested that ketamine may cause transient increases in ICP.[54] However, recent literature clearly suggests that ketamine can be used safely in the setting of controlled ventilation with sedation, with some studies demonstrating a reduction in ICP in both adult and pediatric patient with traumatic brain injury.[55–57]

Ketamine generally increases heart rate and blood pressure and provides bronchodilation due to the release of endogenous catecholamines.[58] *In vitro* and animal studies demonstrate that ketamine has direct negative inotropic properties,[59,60] although indirect sympathomimetic effects from endogenous catecholamine release is generally overriding. However, hypotension and even cardiovascular collapse may occur in patients with diminished myocardial contractility as ketamine's direct negative inotropic properties may predominate when endogenous catecholamine stores have been depleted by stress or chronic illness.[61,62] In a cohort of 12 critically ill adult patients, ketamine administered at a mean dose of 70 mg resulted in significant effects on cardiovascular performance.[61] Fifty-percent of the patients had decreases in ventricular contractility, signified by either an increase in pulmonary capillary wedge pressure or a decrease in left ventricular stroke work. In one-third of the patients, cardiac index fell by more than 10%, mean arterial pressure decreased by $\geq$15%, and there was an increase in intrapulmonary shunt. The authors attributed those findings to a prolonged preoperative stress that blunted the normal physiological response to ketamine. Although other authors have suggested a deleterious effect on pulmonary vascular resistance and a secondary decrease in myocardial performance,[62] more recent data suggest that the effect on pulmonary vasculature is generally negligible.[63]

Given these concerns and the recent report of cardiovascular collapse following ketamine for RCI in two critically ill patients,[12] it appears that the time has come for a re-evaluation of the current practice of RSI and to reconsider the increasing abandonment of etomidate as an effective agent in this scenario. Although the doses used were somewhat higher than those commonly used for RSI (2 mg/kg), the dosing was well within accepted clinical practice parameters. Additionally, although temporally related to the administration of ketamine, other potential causes may have played a primary or secondary role, including relative hypovolemia or alterations in cardiac filling pressures induced by positive pressure ventilation.

CONCLUSION

In the care of critically ill patients, all other resuscitative efforts will fail without effective airway management. In many cases, this requires the use of RSI to safely and effectively control the airway. Given the unpleasant and stressful nature of the procedure, provision of amnesia and analgesia is mandatory, yet, patients who require endotracheal intubation are critically ill, and alterations in cardiovascular performance related to the shift from spontaneous to positive pressure ventilation can have significant effects on cardiovascular performance. These changes may be exacerbated by comorbid conditions, relative hypovolemia, ablation of the sympathetic stress response, lowering of endogenous catecholamines as hypercarbia is corrected, and direct effects of the anesthetic agents used. Most importantly, as noted in recommendations of the American College of Critical Care Medicine, "If possible, volume loading and peripheral or central inotropic/vasoactive drug support is recommended before and during intubation because of relative or absolute hypovolemia, cardiac dysfunction, and the risk of suppressing endogenous stress hormone response with agents that facilitate intubation."[48]

Ketamine has traditionally been associated with a number of contraindications that do not stand up to reasonable examination of available evidence. Of the two medications that are most commonly used to facilitate intubation in patients at risk of hemodynamic compromise, caution regarding the use of etomidate is noted by both American Academy of Pediatrics and the Society of Critical Care Medicine thereby leaving us with ketamine. The sympathomimetic effects of ketamine resulting in enhanced cardiovascular stability make it an extremely useful anesthetic agent. However, in patients with an exhausted endogenous catechol-

amine reserve, the unopposed direct negative inotropic effects of ketamine may lead to cardiovascular compromise.

The previously popular alternative for sedation during endotracheal intubation, etomidate, has fallen out of favor due to its effects on adrenal function. Although there is limited evidence-based medicine to clearly demonstrate that etomidate increases mortality in patients with sepsis, current guidelines caution against its use in this population. Outside of patients with presumed sepsis, etomidate should be considered when choosing an agent for sedation during endotracheal intubation. Most importantly, given the paucity of evidence-based medicine on which to make an effective clinical decision, we would strongly encourage the performance of a future, randomized trial with the power to answer the effect of the agent on mortality. Additional controversy surrounds the issue of whether the effects of etomidate can be negated by the administration of exogenous corticosteroids.[64,65] Furthermore, there appear to be promising new agents in this arena. Carboetomidate, an analog of etomidate with similar hypnotic properties and cardiovascular stability, does not seem to suppress steroid synthesis in animal studies and thus may be a promising alternative for critically ill patients.[66]

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria".

ACKNOWLEDGMENTS Drs. Daniel Scherzer and Mark Leder authored the section on ketamine, and Dr. Tobias authored the section on etomidate.

ABBREVIATIONS AAP, American Academy of Pediatrics; ACTH, adrenocorticotropin hormone; CBF, cerebral blood flow; CMRO2, cerebral metabolic rate for oxygen; CNS, central nervous system; CPP, cerebral perfusion pressure; ICP, intracranial pressure; ICU, intensive care unit; IOP, intraocular pressure; MAP, mean arterial pressure; RSI, rapid sequence intubation; SCCM, Society of Critical Care Medicine; TBI, traumatic brain injury

CORRESPONDENCE Joseph D. Tobias, MD; Chairman, Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, Ohio 43205, e-mail: Joseph.Tobias@Nationwidechildrens.org

REFERENCES

1. Tobias JD. Airway management for pediatric emergencies. *Pediatr Ann*. 1996;25(6):317–320.
2. Tobias JD. Airway management in the pediatric trauma patient. *J Intensive Care Med*. 1998; 13(1):1–14.
3. Tritapepe L, Voci P, Marino P, et al. Calcium chloride minimizes the hemodynamic effects of propofol in patients undergoing coronary artery bypass grafting. *J Cardiothorac Vasc Anesth*. 1999;13(2):150–153.
4. Brussel T, Theissen JL, Vigfusson G, et al. Hemodynamic and cardiodynamic effects of propofol and etomidate: negative inotropic properties of propofol. *Anesth Analg*. 1989; 69(1):35–40.
5. den Brinker M, Hokken-Koelega AC, Hazelzet JA, et al. One single dose of etomidate negatively influences adrenocortical performance for at least 24h in children with meningococcal sepsis. *Intensive Care Med*. 2008;34(1):163–168.
6. Jackson WL Jr. Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock? A critical appraisal. *Chest*. 2005;127(3):1031–1038.
7. Guldner G, Shultz J, Sexton P, et al. Etomidate for rapid sequence intubation in young children: hemodynamic effects and adverse events. *Acad Emerg Med*. 2003;10(2):134–139.
8. Zuckerbraun NS, Pitteti RD, Herr SM, et al. Use of etomidate as an induction agent for rapid sequence intubation in a pediatric emergency department. *Acad Emerg Med*. 2006;13(6):602–609.
9. Sokolove PE, Price DD, Okada P. The safety of etomidate for emergency rapid sequence intubation of pediatric patients. *Pediatr Emerg Care*. 2000;16(1):18–21.
10. Tobias JD. Etomidate: applications in pediatric critical care and pediatric anesthesiology. *Pediatr Crit Care Med*. 2000;1(2):100–106.
11. Tobias JD. Etomidate: applications in pediatric anesthesia and critical care. *J Intensive Care Med*. 1997;12:324–326.
12. Dewhirst E, Frazier WJ, Leder M, et al. Cardiac arrest following ketamine administration for rapid sequence intubation. *J Intensive Care Med*. In press.
13. Janssen PA, Niemegeers CJ, Schellekens KH, Lenaerts FM. Etomidate, *R*-(+)-ethyl-1-(-methyl-benzyl)imidazole-5-carboxylate (R 16659): a potent, short-acting and relatively atoxic intravenous hypnotic agent in rats. *Arzneimittelforschung*. 1971;21(8):1234–1243.
14. Longnecker DE. Stress free: to be or not to be? *Anesthesiology*. 1984;61(6):643–644.
15. Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet*. 1983;321(8336):1270.

16. Watt I, Ledingham IM. Mortality amongst multiple trauma patients admitted to an intensive therapy unit. *Anaesthesia*. 1984;39(10):973–981.
17. Wagner RL, White PF, Kan PB, et al. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. *N Engl J Med*. 1984; 310(22):1415–1421.
18. Forman SA. Clinical and molecular pharmacology of etomidate. *Anesthesiology*. 2011; 114(3):695–707.
19. Absalom A, Pledger D, Kong A. Adrenocortical function in critically ill patients 24 h after a single dose of etomidate. *Anaesthesia*. 1999; 54(9):861–867.
20. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;21; 288(7):862–871.
21. Sprung CL, Annane D, Keh D, et al. CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008; 358(2):111–124.
22. Lipiner-Friedman D, Sprung CL, Laterre PF, et al. Corticus Study Group. Adrenal function in sepsis: the retrospective Corticus cohort study. *Crit Care Med*. 2007;35(4):1012–1018.
23. Annane D. ICU physicians should abandon the use of etomidate! *Intensive Care Med*. 2005; 31(3):325–326.
24. Hildreth AN, Mejia VA, Maxwell RA, et al. Adrenal suppression following a single dose of etomidate for rapid sequence induction: a prospective randomized study. *J Trauma*. 2008;65(3):573–579.
25. Jabre P, Combes X, Lapostolle F, et al. KETASED Collaborative Study Group. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. *Lance*t. 2009; 374(9686):293–300.
26. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Ann Emerg Med*. 2011;57(5):449–461.
27. Filanovsky Y, Miller P, Kao J. Myth: Ketamine should not be used as an induction agent for intubation in patients with head injury. *CJEM*. 2010;12(2):154–157.
28. Bar-Joseph G, Guilburd Y, Tamir A, Guilburd JN. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. *J Neurosurg Pediatr*. 2009; 4(1):40–46
29. Harris JE, Letson RD, Buckley JJ. The use of CI-581, a new parenteral anesthetic, in ophthalmic practice. *Trans Am Ophthalmol Soc*. 1968; 66:206–213.
30. Drayna PC, Estrada C, Wang W, et al. Ketamine sedation is not associated with clinically meaningful elevation of intraocular pressure. *Am J Emerg Med*. In press.
31. Zausig YA, Busse H, Lunz D, et al. Cardiac effects of induction agents in the septic rat heart. *Crit Care*. 2009;13(5):R144.
32. Gelissen HP, Epema AH, Henning RH, et al. Inotropic effects of propofol, thiopental, midazolam, etomidate, and ketamine on isolated human atrial muscle. *Anesthesiology*. 1996; 84(2):397–403.
33. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Ann Emerg Med*. 2011;57(5):449–461.
34. Renou AM, Vernhiet J, Macrez P, et al. Cerebral blood flow and metabolism during etomidate anaesthesia in man. *Br J Anaesth*. 1978;50(10):1047–1051.
35. Moss E, Powell D, Gibson RM, McDowall DG. Effect of etomidate on intracranial pressure and cerebral perfusion pressure. *Br J Anaesth*. 1979; 51(4):347–352.
36. Modica PA, Tempellhoff R. Intracranial pressure during induction of anesthesia and tracheal intubation with etomidate-induced EEG burst suppression. *Can J Anaesth*. 1992;39(3):236–241.
37. Kay B. A clinical assessment of the use of etomidate in children. *Br J Anaesth*. 1976;48(3): 207–210.
38. Kay B. Total intravenous anesthesia with etomidate: evaluation of a practical technique for children. *Acta Anaesth Belg*. 1977;28(2): 115–121.
39. Schechter WS, Kim C, Martinez M, et al. Anaesthetic induction in a child with end-stage cardiomyopathy. *Can J Anaesth*. 1995;42(5 PT 1):404–408.
40. Duthie DJR, Fraser R, Nimmo WS. Effect of induction of anaesthesia with etomidate on corticosteroid synthesis in man. *Br J Anaesth*. 1985;57(2):156–159.
41. Donmez A, Kaya H, Haberal A, et al. The effect of etomidate induction on plasma cortisol levels in children undergoing cardiac surgery. *J Cardiothor Vasc Anesth*. 1998;12(2):182–185.
42. Vinclair M, Broux C, Faure P, et al. Duration of adrenal inhibition following a single dose of etomidate in critically ill patients. *Intensive Care Med*. 2008;34(4):714–719.

43. Ray DC, McKeown DW. Effect of induction agent on vasopressor and steroid use, and outcome in patients with septic shock. *Crit Care*. 2007;11(3):145–147.
44. Cuthbertson BH, Sprung CL, Annane D. The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. *Intensive Care Med*. 2009;35(11):1868–1876.
45. Cotton BA, Guillamondegui OD, Fleming SB, et al. Increased risk of adrenal insufficiency following etomidate exposure in critically injured patients. *Arch Surg*. 2008;143(1):62–67.
46. Markowitz BP. The drug that would not die (though patients receiving it do). *Pediatr Crit Care Med*. 2009;10(3):418–419.
47. Kleinman ME, de Caen AR, Chameides L, et al. Pediatric basic and advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Pediatrics*. 2010;126(5):e1261–e1318.
48. Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med*. 2009;37(2):666–688.
49. Neder Meyer T, Lazaro Da Silva A. Ketamine reduces mortality of severely burnt rats, when compared to midazolam plus fentanyl. *Burns*. 2004;30(5):425–430.
50. Koga K, Ogata M, Takenaka I, et al. Ketamine suppresses tumor necrosis factor alpha activity and mortality in carrageenan-sensitized endotoxin shock model. *Circ Shock*. 1994;44(3):160–168.
51. Taniguchi T, Takemoto Y, Kanakura H, et al. The dose related effects of ketamine on mortality and cytokine response to endotoxin induced shock in rats. *Anesth Analg*. 2003; 97(6):1769–1777.
52. Taniguchi T, Kanakura H, Takemoto Y, et al. The anti-inflammatory effects of ketamine in endotoxemic rats during moderate and mild hypothermia. *Anesth Analg*. 2004;98(4):1114–1120.
53. Taniguchi T, Shibata K, Yamamoto K. Ketamine inhibits endotoxin induced shock in rats. *Anesthesiology*. 2001;95(4):928–932.
54. Takeshita H, Okuda Y, Sari A. The effects of ketamine on cerebral circulation and metabolism in man. *Anesthesiology*. 1972;36(1):69–75.
55. Himmelseher S, Durieux ME. Revising a dogma: ketamine for patients with neurological injury? *Anesth Analg*. 2005;101(2):524–534.
56. Albanèse J, Arnaud S, Rey M, et al. Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. *Anesthesiology*. 1997;87(6):1328–1334.
57. Bar-Joseph G, Guilburd Y, Tamir A, Guilburd JN. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. *J Neurosurg Pediatr*. 2009; 4(1):40–46.
58. Chernow B, Laker R, Creuss D, et al. Plasma, urine, and cerebrospinal fluid catecholamine concentrations during and after ketamine sedation. *Crit Care Med*. 1982;10:600–603.
59. Pagel PS, Kampine JP, Schmeling WT, Warltier DC. Ketamine depresses myocardial contractility as evaluated by the preload recruitable stroke work relationship in chronically instrumented dogs with autonomic nervous system blockade. *Anesthesiology*. 1992;76(4):564–572.
60. Gelissen HP, Epema AH, Henning RH, et al. Inotropic effects of propofol, thiopental, midazolam, etomidate, and ketamine on isolated human atrial muscle. *Anesthesiology*. 1996;84: 397–403.
61. Waxman K, Shoemaker WC, Lippmann M. Cardiovascular effects of anesthetic induction with ketamine. *Anesth Analg*. 1980;59:355–358.
62. Spotoft H, Korshin JD, Sorensen MB, et al. The cardiovascular effects of ketamine used for induction of anesthesia in patients with valvular heart disease. *Can Anaesth Soc J*. 1979;26(6): 463–467.
63. Williams GD, Philip BM, Chu LF, et al. Ketamine does not increase pulmonary vascular resistance in children with pulmonary hypertension undergoing sevoflurane anesthesia and spontaneous ventilation. *Anesth Analg*. 2007; 105(6):1578–1584.
64. Edwin SB, Walker PL. Controversies surrounding the use of etomidate for rapid sequence intubation in patients with suspected sepsis. *Ann Pharmacother*. 2010;44(7-8):1307–1313.
65. Zed PJ, Mabasa VH, Slavik RS, Abu-Laban RB. Etomidate for rapid sequence intubation in the emergency department: is adrenal suppression a concern? *CJEM*. 2006;8(5):347–350.
66. Cotten JF, Forman SA, Laha JK, et al. Carboetomidate: a pyrrole analog of etomidate designed not to suppress adrenocortical function. *Anesthesiology*. 2010;112(3):637–644.