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ETOMIDATE AND CORTICOSTEROID ADMINISTRATION IN THE CRITICALLY ILL PATIENT

By

Julie A. Honeyman

Bachelor of Science in Nursing, University of North Dakota, 2011

An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

Grand Forks, North Dakota

May

2016
Title          Etomidate and Corticosteroid Administration in the Critically Ill Patient
Department    Nursing
Degree        Master of Science

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Abstract

Title: Etomidate and Corticosteroid Administration in the Critically Ill Patient

Background: A 68-year-old male patient undergoing an exploratory laparotomy bowel resection had a recent hospitalization due to sepsis with gram-negative bacteria and diverticulitis of the large colon with perforation. Critically ill patients often undergo surgical procedures and require anesthesia. Etomidate is an induction agent used for general anesthesia and it is most known for its stable hemodynamic profile. Unfortunately, adrenal suppression by etomidate was found as an adverse effect and this finding remarkably limits its use in critically ill patients. Since the discovery of adrenal suppression, the use of corticosteroids to treat this corresponding adrenal suppression has raised the attention of many researchers and clinicians.

Purpose: To evaluate and conclude current recommendation on etomidate use in the critically ill patient and the use of supplemental corticosteroids in preventing adrenal insufficiency caused by etomidate use.

Process: A systematic search was conducted utilizing CINAHL and PubMed for research articles that were published in the last 8 years that pertained to etomidate and corticosteroid administration in the critically ill patient. Information from the review of literature was synthesized to develop evidence-based recommendations for critically ill patients.

Results: Further large, randomized controlled trials are needed to fully determine whether or not administration of corticosteroids will prevent the adrenal insufficiency caused by etomidate use and if etomidate should be administered to the critically ill patient. The most recent and majority of studies found in the literature review indicate corticosteroid use will not prevent the adrenal insufficiency caused by etomidate use and that all together anesthesia providers should consider completely eradicating the use of etomidate in critically ill individuals.

Implications: Informed decision-making should be utilized on a case-by-case basis in regards to etomidate and corticosteroid use in the critically ill. It is essential for anesthesia providers to consider evidence-based recommendations to prevent potential adrenal insufficiency and increased mortality with etomidate use.

Keywords: Etomidate, corticosteroid, adrenal suppression, critically ill patient
Background

Etomidate is a unique induction agent used for general anesthesia and sedation. In 1965, Janssen Pharmaceuticals first introduced etomidate as an antifungal agent, but to their surprise, significant hypnotic activity was noticed. After this revelation, it was introduced into clinical practice in 1972 as a hypnotic agent (Forman, 2011). Etomidate is most known for its hemodynamic stability properties, as it does not inhibit sympathetic tone or myocardial function, like other induction agents. Its benign hemodynamic effect is the main reason this drug became popular for use in critically ill patients. Etomidate has been used in emergency departments, intensive care units, and as the induction medication of choice for critically ill patients.

Unfortunately, adrenal cortical inhibition by etomidate was found as an adverse effect and this finding remarkably limits its use as both an anesthetic and sedative agent. Etomidate inhibits 11β-hydroxylase, which prevents cortisol synthesis. “The inhibition of this enzyme prevents cortisol from responding to stress and triggers a state of adrenal insufficiency” (Black, 2014, p.6). Adrenal suppression can last “6 to 8 hours after a single-induction dose and more than 24 hours after an infusion” (Forman, 2011, p.697). In several studies conducted, the existence of adrenal suppression after etomidate administration showed increased mortality amongst intensive care unit (ICU) patients receiving etomidate infusions for sedation. Due to these findings, long-term etomidate infusions were ceased and no longer recommended. Etomidate’s “drug packet insert was amended to state that etomidate use is approved for induction of general anesthesia and anesthetic maintenance for short operative procedures only” (Forman, 2011, p.698).
Since the discovery of adrenal suppression from etomidate administration, the use of corticosteroids to treat this corresponding adrenal suppression has raised the attention of many researchers and clinicians. In a large multicenter trial, named the CORTICUS study, exposure to single-dose etomidate was a cofounding variable in evaluating the use of supplemental corticosteroids in septic patients with and without adrenal insufficiency. The results of this study “concluded that supplemental steroids after etomidate administration did not improve the long-term outcome of septic shock patients with adrenal insufficiency” (Forman, 2011, p. 698). Conversely, other studies have indicated cortisol replacement therapy could reduce the mortality in critically ill patients receiving etomidate. Due to the conflicting evidence and the growing incidence of critically ill individuals, should anesthesia providers administer corticosteroid replacement therapy after etomidate administration in the critically ill patient?

Case Report

A 68-year-old, 163 cm, 72.5 kg, male patient with a body mass index (BMI) of 27.4 kg/m2, presented with a diagnosis of right lower abdominal pain and was scheduled for an exploratory laparotomy bowel resection. Significant medical history included sepsis due to gram-negative bacteria, diverticulitis of the large colon with perforation, respiratory failure, hypokalemia, and congestive heart failure (CHF). Surgical history included repair of abdominal aortic aneurysm and placement of cardiac stents. Patient had allergies to rosuvastatin, morphine, clopidogrel, simvastatin, and nuts. Home medications consisted of acetylsalicylic acid, famotidine, and naproxen sodium. Pre-operative vital signs consisted of a blood pressure of 100/65, heart rate of 110, respiratory rate of 23, and oxygen saturations of 87%. Pre-operative laboratory data included sodium
of 142, potassium of 2.6, glucose of 142, creatinine of 0.9, blood urea nitrogen (BUN) of 11, chloride of 110, calcium of 8.6, magnesium of 2.3, pH of 7.40, PaCO2 of 37, PaO2 of 50, bicarbonate (HCO3) of 27, hemoglobin of 12.5, hematocrit of 38.3, platelets of 146, white blood count (WBC) of 9.3, partial thromboplastin time (PTT) of 26.6, protime (PT) of 14.9, and international normalized ration (INR) of 1.4. Mallampati classification was assessed as a 3 preoperatively with an ASA classification of 4E.

The plan was to perform general anesthesia with a rapid sequence induction (RSI) with placement of an endotracheal tube (ETT). Preoperatively the patient was given 1 mg midazolam in the pre-operative holding room and continued on bipap therapy with oxygen saturations of 90%. In the operating room, standard noninvasive monitors were applied. Denitrogenation was accomplished with bipap therapy at 100% FiO2 and the patient was induced intravenously (IV) with 50 mg lidocaine, 50 mcg fentanyl, 5 mg rocuronium, 150 mg propofol, and 140 mg succinylcholine prior to placing an 8.0 ETT in 1 attempt with a Mac 3 blade. A grade 1 view was visualized and ETT placement was verified by end-tidal carbon dioxide, bilateral breath sounds, condensation within the tube, and bilateral chest rise. The tube was secured, eyes taped, and anesthetic maintained with desflurane 6.8% with a mixture of 1.0 L/min of oxygen and 1.0 L/min of air.

Mechanical ventilation was applied with volume control (VC) mode, tidal volume of 700 mL, rate of 12/min, and positive end- expiratory pressure (PEEP) of 8 cm/H2O. An arterial line was placed and medication administration was given through a central catheter placed prior in the intensive care unit.

Following induction, the patient was placed in the supine position and positioning concerns were verified with extremities padded. The patient continued to
receive 3.375 g of scheduled zosyn prior to incision. The maintenance phase consisted of fentanyl, rocuronium, potassium chloride, albumin, and a phenylephrine infusion. A total of 2.8 liters of crystalloid solution was given intra-operatively, blood loss was estimated at 175 mL, and urine output was 250 mL. Post-operative nausea and vomiting prophylaxis was performed with 4 mg ondansetron and 8 mg dexamethasone. Due to decreased oxygen saturations and inadequate arterial blood gases, the patient was left sedated and intubated following the procedure. The patient was transferred to the surgical critical care unit (SCCU) in stable condition. The duration of the procedure was approximately 2.5 hours.

The patient remained in the SCCU where he remained sedated and intubated 4 days post-operatively due to hypoxic respiratory failure and acute exacerbation of CHF. After the patient was extubated and in stable condition, he was transferred to the medical floor where he remained for 4 additional days post-operatively. The patient was then discharged home on postoperative day 8.

**Discussion**

As a result of etomidate’s hemodynamic tolerance, it is a first-line anesthetic agent used to facilitate endotracheal intubation in hemodynamically unstable patients and has emerged as an agent of choice for critically ill patients. “However, single-dose etomidate has been found to block cortisol synthesis by specifically inhibiting the activity of 11-β-hydroxylase, which is responsible for the conversion of 11-β-deoxycortisol into cortisol in the adrenal gland” (Payen, et al., 2012, p. 29). This enzyme inhibition results in primary adrenal insufficiency with effects lasting up to 48 hours post-administration (Payen, et al., 2012). “Such adrenal insufficiency is associated with higher rates of
mortality and morbidity in critically ill individuals and raises concerns over the potential for etomidate to worsen patient outcomes” (Payen, et al., 2012, p. 29). However, due to etomidate’s hemodynamic stability properties, it raises the question of whether or not to eliminate the use of etomidate all together or to add concomitant administration of corticosteroids to prevent acute adrenal insufficiency.

**Etomidate Administration**

Etomidate is a common IV induction agent used in general anesthesia and in the past has been used as a sedative in the ICU. It is a “carboxylated imidazole derivative that was synthesized in 1965 and introduced to European anesthesia practice in 1972” (Nagelhout & Plaus, 2014, p. 110). Etomidate consists of two isomers, but only the R(+) isomer demonstrates hypnotic characteristics. It is supplied as a “2mg/mL preparation with each milliliter containing 35% propylene glycol as a solvent and has a pH of 8.1 and a pKa of 4.2” (Nagelhout & Plaus, 2014, p. 110). The IV induction dose of etomidate for general anesthesia is 0.2-0.3 mg/kg. The drug’s hallmark advantage over other induction medications is that it promotes cardiovascular stability, which is the main reason it is often the drug of choice in certain patient populations.

**Pharmacokinetics**

The mechanism of action of etomidate involves depression of the reticular activating system and inhibition of GABA. “Etomidate’s R(+) isomer binds to a subunit of the GABA\textsubscript{A} receptor, which increases the receptor’s affinity for the inhibitory neurotransmitter, GABA” (Butterworth, Mackey, & Wasnick, 2013, p. 184). After IV injection, it has a peak onset time of 1 minute. “Shortly after administration, the brain concentration rises rapidly because of the drug’s lipid solubility and over the next several
minutes, extensive redistribution to other organs and tissues occurs and the patient regains consciousness” (Nagelhout & Plaus, 2014, p. 111). Etomidate is rapidly metabolized in the liver by hepatic enzymes and plasma esterases via hydrolysis to form inactive metabolites and has an elimination half-life of 2 to 5 hours (Black, 2014). “Approximately 10% of the administered dose can be recovered in bile, 13% be recovered in feces, and the remainder of the metabolites are eliminated by the kidney” (Nagelhout & Plaus, 2014, p. 111). The rapid redistribution of etomidate accounts for its extremely short duration of action.

**Pharmacodynamics**

Central nervous system (CNS) effects of etomidate include decreased cerebral blood flow, cerebral metabolic rate of oxygen consumption and intracranial pressure, and maintained cerebral perfusion pressure (Forman, 2011). A negative CNS characteristic of etomidate is its excitatory phenomenon of tremors, known as myoclonia (Stoeltig & Hillier, 2006). The myoclonia is known to be so severe that it can resemble seizures. “The origin of these muscle movements is thought to be related to uneven drug distribution into the brainstem or deep cerebral structures and not to CNS stimulation” (Nagelhout & Plaus, 2014, p. 111). Pretreatment with small doses of etomidate, dexmedetomidine, midazolam, rocuronium, and lidocaine are all effective in reducing myoclonia.

The primary advantage of etomidate is the hemodynamic stability it produces upon induction. “Minimal changes in heart rate, blood pressure, central venous pressure, and intrapulmonary shunting have been demonstrated after administration” (Nagelhout & Plaus, 2014, p. 111). A minor decrease in blood pressure is theorized to be due to
decreases in systemic vascular resistance. “The hemodynamic stability seen with etomidate has been attributed to a unique lack of depression of sympathetic nervous system and baroreceptor function” (Nagelhout & Plaus, 2014, p. 111). “Myocardial oxygen supply and demand are kept constant by a balance of decreased myocardial blood flow and decreased oxygen consumption” (Nagelhout & Plaus, 2014, p. 111). No significant cardiac dysrhythmias are connected with its use.


Adrenal Suppression

During the 1980’s, etomidate began to receive much attention regarding the adrenal cortical inhibition it produced. Since this time, etomidate has been widely studied for both its beneficial and detrimental effects. The adrenal suppression it creates significantly limits its clinical use. Researches have found an increased mortality rate in critically ill patients who received etomidate infusions (Forman, 2011). “This phenomenon was attributed to adrenocortical hypofunction, demonstrated by decreased levels of plasma cortisol” (Nagelhout & Plaus, 2014, p. 112). “Multiple studies have shown adrenal hormone levels to be decreased for up to 8 to 24 hours after a single-induction dose or more than 24 hours with an infusion” (Stoelting & Hillier, 2006, p. 166). These effects are caused by a reversible dose-dependent inhibition of adrenal steroidogenesis. The enzymes inhibited are the cytochrome P-450-dependent
mitochondrial enzymes and 11-β-hydroxylase (Nagelhout & Plaus, 2014). This inhibition results in an increase in cortisol precursors but a decrease in cortisol, aldosterone, and corticosterone levels (Forman, 2011). This enzyme inhibition results in decreased ascorbic acid synthesis, which is necessary for steroid production” (Nagelhout & Plaus, 2014, p. 112).

**Side-Effects/Contraindications**

Etomidate is contraindicated in patients with a known sensitivity, adrenal suppression, and acute porphyrias (Forman, 2011). It is associated with no analgesic properties. Common side effects include pain on injection, thrombophlebitis, myoclonia, nausea and vomiting, and most noting adrenocortical suppression (Forman, 2011).

**Hypothalamic-Pituitary-Adrenal (HPA) System**

The HPA axis is organized into three distinct regions: hypothalamus, pituitary gland, and adrenal glands. “Specifically, the paraventricular nucleus is the hypothalamic region that uses corticotrophin-releasing hormone (CRH) to stimulate the pituitary” (Smith & Vale, 2006, p.385). Upon stimulation, the anterior pituitary releases adrenocorticotropic hormone (ACTH), which is transported in the general circulation to the adrenal cortex of the adrenal glands. “The adrenal glands rapidly synthesize and release cortisol and other hormones into the blood where it participates in the response to stress and maintenance of homeostasis throughout the body” (Smith & Vale, 2006, p.386). The adrenal glands are the effector organ of the HPA axis and its actions are essential to maintain homeostasis (Smith & Vale, 2006).
**Adrenal Cortex & Corticosteroids**

The adrenal glands are located at the superior facet of each kidney and consist of the adrenal cortex and medulla. The adrenal medulla encompasses the central 20% of the adrenal gland and secretes the hormones epinephrine and norepinephrine. The adrenal cortex comprises the outer part of the adrenal gland and secretes three main types of hormones: mineralocorticoids, glucocorticoids, and androgenic hormones (Nagelhout & Plaus, 2014). The adrenal cortex is divided into three zones and includes the outermost zona gomerulosa that secretes mineralcorticoids, the middle zona fasciculata that secretes glucocorticoids, and the innermost zona reticularis that secretes androgens and estrogens (Stoelting & Hillier, 2006).

The adrenal cortex produces more than 30 types of steroid hormones. “All hormones secreted from the adrenal cortex have a steroidal structure and share a common cholesterol backbone” (Nagelhout & Plaus, 2014, p.862). As a unit, these hormones are termed corticosteroids. The two major classes of corticosteroids are mineralocorticoids and glucocorticoids. “Mineralocorticoids influence the plasma concentrations of sodium and potassium ions, whereas glucocorticoids influence carbohydrate, fat, and protein metabolism, as well as exhibiting anti-inflammatory effects” (Stoelting & Hillier, 2006, p. 809). Aldosterone is the primary mineralocorticoid, while cortisol is the main glucocorticoid.

**Corticosteroid: Mineralocorticoids**

Mineralocorticoids, mainly aldosterone, play a vital role in regulating potassium and sodium levels and total body fluid balance. “They are required for life and with a total loss of mineralocorticoid secretion; death would ensue within days without
treatment” (Nagelhout & Plaus, 2014, p. 863). Mineralocorticoids are produced in the zona glomerulosa, the outermost layer of the adrenal cortex. An example of an endogenous mineralocorticoid with no glucocorticoid properties is desoxycorticosterone. An example of an exogenous mineralocorticoid is fludrocortisone, which contains minute glucocorticoid properties. Mineralocorticoid inhibitors consist of spironolactone and eplerenone (Stoelting & Hillier, 2006). Control of aldosterone secretion is independent of ACTH control. “After secretion from the adrenal cortex, aldosterone circulates 60% bound to serum proteins and has a relatively short half-life of about 20 minutes” (Nagelhout & Plaus, 2014, p. 863). The four main stimulants of aldosterone release are hyperkalemia, angiotensin II, hyponatremia, and ACTH (Nagelhout & Plaus, 2014). Aldosterone secretion is regulated by the renin angiotensin mechanism and by blood levels of potassium. Increased levels of aldosterone promote sodium retention by the distal tubules of the kidney while increasing urinary losses of potassium” (Mattson Porth & Matfin, 2009).

**Corticosteroid: Glucocorticoids**

Glucocorticoids are produced in the zona fasciculata and zona reticularis of the adrenal gland. Cortisol, also known as hydrocortisone, is the main glucocorticoid and it accounts for 95% of the glucocorticoids released from the adrenal cortex (Nagelhout & Plaus, 2014). ACTH mainly regulates cortisol secretion and in turn, cortisol is the most potent controller of ACTH. “Cortisol has a direct negative feedback effect on the hypothalamus, inhibiting the release of CRH, and on the anterior lobe of the pituitary gland, decreasing ACTH synthesis and release” (Nagelhout & Plaus, 2014, p. 863). When cortisol concentration is high, the feedback system reduces ACTH production and vice
versa. ACTH levels have significant diurnal variation and tend to reach their peak in the early morning and decline as the day advances. “This variation appears to be due to rhythmic activity in the CNS, which causes bursts of CRH secretion and, in turn, ACTH secretion” (Mattson Porth & Matfin, 2009, p. 739). “The rhythm may be changed by physical and psychological stresses, endogenous depression, manic-depressive psychosis, and liver disease or other conditions that affect cortisol metabolism” (Mattson Porth & Matfin, 2009, p. 739).

Under normal circumstances, cortisol production is 15 to 30 mg daily. Many aspects of life can increase the amount of cortisol produced and can broadly be categorized into physical and mental stress. “Stress, including surgery, typically raises cortisol production levels to more than 100 mg/day” (Nagelhout & Plaus, 2014, p. 863). The normal cortisol blood concentration averages 12 mcg/dL, and this may increase to 30 to 50 mcg/dL during and after major surgery” (Nagelhout & Plaus, 2014, p. 863).

After release from the adrenal cortex, cortisol circulates in blood in the form of either free or bound cortisol. If bound, cortisol is attached to cortisol-binding globulin or albumin. “Approximately 90% to 95% of cortisol is transported in the bound form and 6% is free” (Nagelhout & Plaus, 2014, p. 863). “Like other steroid hormones, cortisol exerts its effects by binding to target cell nuclear receptors and alters gene transcription and translation” (Nagelhout & Plaus, 2014, p. 863). Most of the metabolic effects of cortisol are not instantaneous and may take several hours to fully foster. Cortisol is inactivated mainly in the kidney and liver and excreted in the urine as 17-hydroxycorticosteroids” (Nagelhout & Plaus, 2014, p. 863).
Glucocorticoids execute a crucial function in response to stress and are critical for survival. When created as part of the stress response, glucocorticoids assist in regulating metabolic, immunologic, and anti-inflammatory functions. The metabolic functions of cortisol involves stimulating glucose production by the liver, promoting protein breakdown, and causing mobilization of fatty acids (Mattson Porth & Matfin, 2009). “As glucose production by the liver rises and peripheral glucose use falls, a moderate resistance to insulin develops, and an increase in blood glucose develops” (Mattson Porth & Matfin, 2009, p.739). Many of the immunologic and anti-inflammatory actions accredited to cortisol result from the administration of pharmacologic levels of the hormone. After administration, the increased amount of cortisol works by “blocking inflammation at an early stage by decreasing capillary permeability and stabilizing the lysosomal membranes so that inflammatory mediators are not released” (Mattson Porth & Matfin, 2009, p.739). In addition, “cortisol suppresses the immune response by reducing humoral and cell-mediated immunity and inhibiting prostaglandin synthesis, which may account for its anti-inflammatory actions” (Mattson Porth & Matfin, 2009, p.739).

A characteristic of long-term pharmacologic preparations of glucocorticoid therapy is the adrenal insufficiency produced from the withdrawal of the drugs. The deficiency results from the suppression of the HPA system. “Chronic HPA suppression causes atrophy of the adrenal gland, and the abrupt withdrawal of pharmacologic preparations of glucocorticoids can cause acute adrenal insufficiency” (Mattson Porth & Matfin, 2009, p.739). After chronic HPA suppression and abrupt withdrawal, recovery of adrenal functioning can take up to 12 months or even more (Mattson Porth & Matfin, 2009). Therefore, a sufficient replacement should be provided to patients who lack
adrenal function, whether it be pharmacological or pathophysiologic in nature, and who are acutely ill or undergoing major surgeries.

A variety of synthetic glucocorticoids have been created for therapeutic use and differ in both pharmacokinetics and pharmacodynamics. Glucocorticoid potency, duration of effect, and the overlapping mineralocorticoid potency vary between each drug. “Cortisol is the standard of comparison for glucocorticoid potency and hydrocortisone is the name used for pharmaceutical preparations of cortisol” (Stoelting & Hillier, 2006, p.810). Examples of glucocorticoids include: cortisol, cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, and beclometasone (Stoelting & Hillier, 2006). In comparison, hydrocortisone’s glucocorticoid and mineralocorticoid potency is equal and has a short duration of action, while dexamethasone has only glucocorticoid properties with no mineralocorticoid involvement and a long duration of action. For the sole fact hydrocortisone has additional mineralocorticoid effects, while dexamethasone does not, it is often the drug of choice when supplemental replacement is needed in individual cases where high stress environments are encountered or long-term use has been identified.

**The Critically Ill Patient**

“Sepsis, severe sepsis, and septic shock are all inflammatory states resulting from a systemic response to bacterial infection” (Maggio & Carvalho, 2015). Sepsis embodies a gamut of disease ranging from systemic inflammatory response syndrome (SIRS) to septic shock. SIRS is a collection of symptoms of systemic inflammation that may or may not be the result of an infection. Manifestations of SIRS includes a “temperature greater than 38 degrees Celsius, heart rate greater than 90 beats per minutes, respiratory
rate greater than 20 breaths per minutes or PaCO2 less than 32 mmHg, and a WBC count greater than 12,000 cells/μL or less than 4,000 cells/μL” (Maggio & Carvalho, 2015). Sepsis is defined as greater than or equal to 2 SIRS criteria with known or suspected infection and severe sepsis is sepsis with organ dysfunction (Maggio & Carvalho, 2015). Lastly, septic shock is “sepsis with refractory hypotension and impaired organ perfusion despite adequate fluid resuscitation” (Maggio & Carvalho, 2015).

“Most cases of septic shock are caused by hospital-acquired gram-negative bacilli or gram-positive cocci and often occur in immunocompromised patients and patients with chronic and debilitating diseases” (Maggio & Carvalho, 2015). Septic shock appears more often in the populations of neonates, elderly, and childbearing women. Predisposing factors include “diabetes mellitus, cirrhosis, leukopenia, prior treatment with antibiotics or corticosteroids, and invasive devices such as endotracheal tubes, vascular or urinary catheters, drainage tubes, and other foreign materials” (Maggio & Carvalho, 2015). Common causative sites of infection include the lungs and the urinary, biliary, and gastrointestinal tracts.

The pathophysiology of septic shock is not completely known or understood. Researchers do know “an inflammatory stimulus triggers production of pro-inflammatory mediators, which cause neutrophil–endothelial cell adhesion, activation of the clotting cascade, and generation of microthrombi” (Maggio & Carvalho, 2015). Pro-inflammatory mediators involved include tumor necrosis factors (TNF), interleukin-1 (IL-1), leukotrienes, lipoxygenase, histamine, bradykinin, serotonin, and interleukin-2 (IL-2) (Maggio & Carvalho, 2015). The aforementioned mediators are opposed by anti-inflammatory mediators, such as interleukin-4 (IL-4) and interleukin-10 (IL-10), resulting
in a negative feedback mechanism. Initially, warm shock occurs by evidence of arteries and arterioles dilating, decreasing peripheral arterial resistance, and increasing cardiac output (Maggio & Carvalho, 2015). During the increase in cardiac output, vasoactive mediators cause blood flow to bypass capillary exchange vessels. As a result, poor capillary flow from shunting, along with capillary obstruction by microthrombi, decreases delivery of oxygen and impairs removal of carbon dioxide and waste products (Maggio & Carvalho, 2015). Decreased perfusion then causes organ dysfunction to one or more organs, including the kidneys, lungs, liver, brain, and heart. Coagulopathy may also develop because of intravascular coagulation with consumption of major clotting factors. Following the warm stage, cardiac output may decrease, blood pressure fall, and typical symptoms of shock will appear.

Signs and symptoms of sepsis can initially be subtle and easily mistaken for manifestations of other diseases. With sepsis, patients typically manifest with fever, tachycardia, diaphoresis, and tachypnea, while often times blood pressure will remain within normal limits (Maggio & Carvalho, 2015). As severe sepsis or septic shock begins to develop, an early sign encountered may be confusion or a decreased level of consciousness. In this state, blood pressure will be decreased, yet the skin will appear unexpectedly warm initially. Later, extremities become cool and pale, with peripheral cyanosis and mottling occurring. Organ dysfunction will ensue from the inadequate perfusion and cause additional signs and symptoms specific to the organ involved. Treatment includes restoring perfusion with intravenous fluids, vasopressors, oxygen therapy, broad-spectrum antibiotics, source control, and other supportive measurements, such as insulin and corticosteroids (Maggio & Carvalho, 2015).


**Etomidate & Corticosteroid Administration**

Evidence has concluded etomidate is capable of causing acute adrenal insufficiency and even a single-dose has been demonstrated to inhibit cortisol production for up to 48 hours (Marik, 2012). The idea of corticosteroid supplementation after etomidate use has been proposed to combat the adrenal insufficiency (Marik, 2012). A randomized, controlled, double-blind study conducted in 2012 by Payen, et al. provided some guidance to this discussion. “The authors’ research disclosed that a moderate-dose of hydrocortisone, 200-300 mg/day, has been successfully proposed to overcome critical illness-related adrenal insufficiency, particularly in septic patients responding poorly to fluid resuscitation and vasopressor agents. The more rapid resolution of septic shock and reduction of norepinephrine doses suggested the potential usefulness of moderate-dose hydrocortisone in patients with vasopressor-dependent septic shock. However, the effectiveness of moderate-dose hydrocortisone has never been prospectively tested during the period of etomidate-related adrenal insufficiency. Therefore, this study sought to investigate the effectiveness of moderate-dose hydrocortisone at decreasing the proportion of vasopressor-dependent patients without septic shock after single-dose etomidate” (Payen, et al., 2012, p.29).

Payen and colleagues study sought to investigate the effects of moderate-dose hydrocortisone on hemodynamic status in critically ill patients throughout the period of etomidate-related adrenal insufficiency. The study involved 97 critically ill patients to receive a 42-hour continuous infusion of either hydrocortisone or a placebo after a single intubating dose of etomidate. The authors excluded individuals who had known HPA axis dysfunction and prior use of corticosteroids. Based on a corticotropin-stimulation test and
measurement of 11-β-deoxycortisol concentration, 87% of patients fulfilled the diagnostic criteria for etomidate-related adrenal insufficiency 6 hours after the dose of etomidate (Payen, et al., 2012).

Payen and associates study concluded critically ill patients without septic shock did not benefit from hydrocortisone administration to overcome etomidate-related insufficiency and replacement doses of hydrocortisone are not required after a single dose of etomidate. There were no changes associated with the use of moderate-dose hydrocortisone, nor did it affect the ICU length of stay, the number of days on the ventilator, or the 28-day mortality. Following the release of this study, Dr. Marik and Dr. Dmello wrote two separate editorials, both agreeing with Payen and colleagues. Dr. Marik wrote there was no difference found between the group that had received the hydrocortisone and the placebo group” (Marik, 2012). They both advised against the use of routine steroid supplementation after etomidate use in critically ill patients, as it does not appear to improve mortality. Dr. Marik and Dr. Dmello purposed these conclusions might even go further and additionally apply to patients with severe sepsis and septic shock.

An observational study conducted in 2012 by Jung, et al. focused on septic shock patients treated with hydrocortisone after etomidate administration. “The aim of this study was to compare septic shock patients who received etomidate versus another induction drug both for short-term safety and long-term outcomes” (Jung, et al., 2012, p.1). The study consisted of 60 patients in the etomidate cohort and 42 patients in the non-etomidate cohort. Critical illness-related corticosteroid insufficiency was 79% in the etomidate cohort and 52% in the non-etomidate cohort. This study suggested “septic
shock patients treated with hydrocortisone after etomidate use was not associated with a decrease of life-threatening complications following intubation in comparison with other hypnotics” (Jung, et al., 2012, p. 7). It also concluded that etomidate was associated with a “longer period of shock and a higher cumulative dose of hydrocortisone than patients intubated with another hypnotic” (Jung, et al, 2012, p.8).

“The Corticosteroid Therapy of Septic Shock (CORTICUS) study was a prospective, multicentered, randomized, double-blind, placebo-controlled trial” (Toma, Stone, Green, & Gray, 2011, p.273). Patients were recruited from 52 ICU’s in nine countries from March 2002 to November 2005. “Patients were 18 years of age or older with clinical evidence of infection, evidence of systemic response to infection, and hypoperfusion or organ dysfunction attributable to sepsis” (Toma, et al., 2011, p.273). Five hundred patients were randomized to receive either hydrocortisone or placebo and all patients were to undergo a corticotropin stimulation test prior to initiation of therapy. “The results of this study concluded supplementation of hydrocortisone to compensate for the potential negative effects of etomidate on outcomes does not seem to work” (Van Dan Heuvel, et al., 2013, p.407). “Hydorcortisone administration had no effect on outcome in these patients, and therefore the use of hydrocortisone to treat etomidate related adrenal insufficiency should be reevaluated” (Cuthbertson, et al., 2009, p. 1874). The article also included tips from other current evidence and indicated patients with septic shock that receive corticosteroids may benefit from a faster resolution of hypotension if corticosteroids are administered within the first 8 hours of the diagnosis of sepsis. Although, this potential benefit has to be weighed against the possible increase in superinfection and recurrent shock (Toma, et al., 2011).
Therefore, informed decision-making should be utilized on a case-by-case basis when using etomidate in critically ill patients with severe sepsis or septic shock, and perhaps corticosteroids should be reserved for refractory shock, independent of etomidate use. It is purposed that the “efficacy of corticosteroids may be related to enhancing the hemodynamic response to norepinephrine rather than the mitigation of etomidate-related 11-β-hydroxylase inhibition” (Dmello, 2012, p.2004). Due to the lack of abundant studies indicating a potential benefit of corticosteroid use, it is apparent that future randomized controlled studies need to be conducted to confirm these findings.

**Etomidate & Critically Ill Patients**

The dispute over etomidate use in critically ill patients has been a topic of debate for years. “As a result of its excellent hemodynamic tolerance, etomidate is a first-line anesthetic agent used to facilitate endotracheal intubation in hemodynamically unstable patients and has emerged as an agent of choice for RSI in critically ill patients.” (Payen, et al., 2012, p.29). However, single dose etomidate blocks cortisol synthesis and causes primary adrenal insufficiency with effects lasting up to 48 hours post-administration (Payen, et al., 2012). “Such adrenal insufficiency is associated with higher rates of mortality and morbidity in the ICU, raising concerns over the potential for etomidate to worsen patient outcome as was shown in patients with septic shock or with trauma” (Payen, et al., 2012, p. 29). Etomidate is recognized to cause adrenal suppression in both elective surgical patients and more profoundly in the critically ill.

In critically ill patients, induction with etomidate is hypothesized to be associated with an increased risk of mortality. “Previous randomized studies suggest a modest trend toward an increased risk of death among etomidate recipients; however, this relationship
has not been measured with great statistical precision” (Sunshine, et al., 2013, p. 639). A study conducted in 2013 by Sunshine, et al. aimed to test whether etomidate is associated with an increased risk of hospital mortality and other clinical outcomes in critically ill patients. The study was a “retrospective cohort study conducted 2001 to 2005 and consisted of 824 subjects requiring mechanical ventilation, who underwent adrenal function testing in the ICU’s of 2 academic medical centers” (Sunshine, et al., 2013, p. 639). The primary outcome was in-hospital mortality, comparing subjects given etomidate to those given an alternative induction agent. The results of the study concluded the “relative risk of death among the etomidate recipients was higher than that of subjects given an alternative agent” (Sunshine, et al., 2013, p.645). The authors of this study also added these findings are similar to the collective results of smaller randomized trials conducted to date.

In a 2013 review, Van Den Heuvel and colleagues sought out to evaluate the most recent publications in the long-lived debate over the use of etomidate in critically ill septic patients. In the review, the authors discussed three recent meta-analyses of randomized controlled trials and observational studies. In the first meta-analysis, “five studies were identified that assessed mortality, in which a total of 865 subjects were included” (Van Dan Heuvel, et al., 2013, p.407). This analysis indicated that subjects who received etomidate were more likely to die. In the same meta-analysis, “seven studies addressed the development of adrenal suppression associated with the administration of etomidate and 1303 subjects were included” (Van Dan Heuvel, et al., 2013, p.407). Etomidate administration increased the likelihood of developing adrenal insufficiency. A second recent meta-analysis came to the same conclusion. Lastly, in the
largest meta-analysis including critically ill patients with and without sepsis, 21 articles were evaluated. “The meta-analysis compared etomidate versus non-etomidate anesthesia and demonstrated an increased risk ratio for adrenal insufficiency and an increased risk ratio for mortality” (Van Dan Heuvel, et al., 2013, p.407). Therefore, all three meta-analyses concluded findings of adrenal insufficiency and an increase in mortality after use of etomidate (Van Den Heuvel, et al., 2013).

Dr. Brian Fengler wrote an article in the *American Journal of Emergency Medicine* discussing previous studies conducted in the emergency department (ED). His summarized research indicated that healthy, elective surgical patients who received etomidate, only showed a transient and not clinically significant adrenal suppression (Fengler, 2007). However, Dr. Fengler found “retrospective studies in the pediatric and adult intensive care literature that showed an association between a single induction dose of etomidate in critically ill septic patients and sustained suppression of the adrenal axis with an increase in mortality” (Fengler, 2007, p. 229). Along with Dr. Fengler’s findings and the previously mentioned CORTICUS study, both concluded patients who received etomidate had an increased risk of mortality compared to those with an alternative induction agent. In addition, a letter to the editor relating to the CORTICUS study by Dr. Paul Dean also agreed. Dr. Dean concluded “etomidate no longer has a role as the induction agent of choice in patients with septic shock in the anesthetic room or intensive care unit” (Dean, 2012).

In the previous studies described, it is apparent there is a lack of cause and effect when attempting to specifically link etomidate and increased mortality. There are many other factors in the critically ill patient that could also contribute to increased mortality.
Further studies are needed to address this fact and determine if the adrenal insufficiency leads to increased mortality itself or if it more multifactorial in nature.

In opposition to the above-mentioned conclusions, two studies were found to have the opposite conclusion. The first study was a retrospective 18-month cohort study performed in a multidisciplinary ICU of an academic tertiary care institution. Patients with severe sepsis and septic shock who were intubated and mechanically ventilated were identified and grouped as having received single-dose etomidate during intubation or not. Hospital mortality, ICU length of stay, number of ventilator day, vasopressor use, and demographic and clinical variables were recorded (Dmello, Taylor, O’Brien, & Matuschak, 2010). Two hundred twenty-four patients were identified and 113 received etomidate. “The results of this study indicated single-dose etomidate used during RSI in critically ill patients with severe sepsis and septic shock was not associated with increased mortality, vasopressor use, ICU length of stay, or number of ventilator days” (Dmello, et al., 2010, p. 1327). The second study conducted by Hohl et al. in 2009, was a quantitative and qualitative systematic review of the literature. These individuals reviewed 3,083 titles and only 20 met their inclusion criteria. There were many limitations listed in this study. Hohl et al. concluded “etomidate suppresses adrenal function transiently without demonstrating a significant effect on mortality” (Hohl, et al., 2009, p.105).

Large, randomized controlled trials and studies specifically linking the cause and effect of etomidate and mortality are needed to finalize the role of etomidate in critically ill patients. Many studies advise against the use of etomidate in critically ill individuals but the propounding data to support this is not all the way there yet. Many studies suggest
practitioners to seek out alternative induction techniques for hemodynamically unstable patients, including a high opioid and low dose propofol infusion or a combination of ketamine and propofol in order to prevent post-induction hypotension (Black, 2014).

**Conclusion**

In conclusion, additional large, randomized controlled studies are needed to provide a definite conclusion to the question of whether or not etomidate should be administered to the critically ill patient and if administration of corticosteroids will prevent adrenal insufficiency after etomidate use. The majority of recent research indicates corticosteroid use will not prevent the adrenal insufficiency caused by etomidate use and that all together anesthesia providers should consider completely eradicating the use of etomidate in critically ill individuals. In the aforementioned case study, etomidate or corticosteroid administration was not chosen for the critically ill individual for these reasons. Furthermore, it is apparent the dilemma anesthesia personnel face due to the complexity associated with the critically ill patient. However, without definitive evidence supporting the use of etomidate in the critically ill or the use of corticosteroid replacement following etomidate use, it would be prudent for the anesthesia provider to consider using other safer alternatives.
References


Etomidate and Corticosteroid Administration in the Critically Ill Patient
Julie Honeyman, SRNA

History of Etomidate
- In 1965, Janssen Pharmaceuticals first introduced it as an antifungal agent
- Presented into clinical practice in 1972 as a hypnotic agent
- Most known for its stable hemodynamic properties
- Drug of choice for critically ill patients for this sole fact

Etomidate and Adrenal Suppression
- Adrenal suppression was discovered as an adverse effect
- Inhibits 11β-hydroxylase
- Persists 6-8 hours after a single-induction dose and more than 24 hours after an infusion
- Administration of corticosteroids has raised the attention of many researchers and clinicians

Review of Literature
- A review of literature was conducted using the Harley E. French Library to determine current recommendations on the following question:
  - Should anesthesia providers administer corticosteroid replacement therapy after Etomidate administration and should Etomidate be used in critically ill patients?

Case Information
- Surgical Procedure: Exploratory laparotomy/bowel resection
- Age: 68 year-old
- Weight/Height/BMI: 75 kg, 163 cm, 27.4 kg/m²
- Gender: Male
- Allergies: Rosuvastatin, Morphine, Clopidogrel, Simvastatin, and nuts
- ASA: 4E

Preoperative Evaluation
- Significant Medical History: Sepsis due to gram-negative bacteria, diverticulitis of large colon with perforation, respiratory failure, hypokalemia, and CHF
- Surgical History: AAA repair and cardiac stents
- Home Medications: Acetylsalicylic acid, Famotidine, and Naproxen Sodium
- Pre-op VS: BP 100/65, HR 110, RR 23, SpO2 87%
- Airway Evaluation: M III, TM distance >3 FB, mouth opening >3 FB, and full neck ROM
Preoperative Evaluation

**Laboratory Data:**
- Na: 142 mEq/L
- K: 2.6 mEq/L
- Glucose: 142 mg/dL
- Cl: 110 mmol/L
- Ca: 8.6 mg/dL
- Mg: 2.3 mEq/L
- Creatinine: 0.9 mg/dL
- BUN: 11 mg/dL
- pH: 7.40
- pCO2: 37
- pO2: 50
- HCO3: 27
- Hgb: 12.5 g/dL
- Hct: 38.3%
- Pts: 146

Anesthetic Course

**GETA with RSI:** (Emergent case)
- Midazolam: 1 mg
- Denitrogenation with bipap therapy
- Fentanyl: 50 mcg
- Lidocaine: 50 mg
- Rocuronium: 5 mg
- Propofol: 150 mg
- Succinychloline: 140 mg
- Desflurane via Mac 3 blade
- Central line present

**Additional Medications:**
- Zoyn: 3.375 g
- Fentanyl
- Rocuronium
- Potassium Chloride
- Albumin
- Phenylephrine infusion
- Ondansetron 4 mg
- Dexamethasone 8 mg

Intraoperative Issues

- Continued tachycardia → IV Fluids and PRN fentanyl
- Hypotension encountered → IV Fluids and phenylephrine infusion
- Decreased SpO2 → 100% O2, ABG’s drawn, and tentative plan to keep patient intubated at the end of the procedure

Postoperative - SCCU

- Decreased SpO2 and inadequate ABG’s
- Transferred to SCCU where he remained intubated 4 days due to hypoxic respiratory failure
- Transferred to medical floor for 4 additional days
- Discharged home on post-operative day 8

**Case Totals:**
- Urine output: 250 mL
- EBL: 175 mL
- LR: 2.8 L
- Case duration: 2.5 hours

Etomidate’s MOA

- Involves depression of the reticular activating system and inhibition of GABA
- R(+) isomer binds to the subunit of the GABA receptor, which increases the receptor’s affinity for the inhibitory neurotransmitter, GABA
- First-line anesthetic agent in hemodynamically unstable patients
- Agent of choice for critically ill individuals

Etomidate

- It has been widely studied for both its beneficial and detrimental effects
- A single dose has been found to block cortisol synthesis by specifically inhibiting the activity of 11β-hydroxylase
- Adrenal insufficiency has been documented for up to 48 hours post-administration after a single dose!
- Increased mortality rate in critically ill patients receiving infusions

Nagelhout & Plaus, 2014; Bauerworth, Mavanda, & Wasnick, 2013
Corticosteroids
- Adrenal cortex secretes three main types of hormones: mineralocorticoids, glucocorticoids, and androgenic hormones
- All hormones produced are termed corticosteroids
- Two major classes are mineralocorticoids and glucocorticoids
- Mineralocorticoids influence the plasma concentration of sodium and potassium ions
- Glucocorticoids influence carbohydrate, fat, and protein metabolism, as well as exhibiting anti-inflammatory effects
- Aldosterone is the primary mineralocorticoid
- Cortisol is the main glucocorticoid

Glucocorticoids
- Execute a crucial function in response to stress and are critical for survival
- When created as part of the stress response, they assist in regulating metabolic, immunologic, and anti-inflammatory functions
- Cortisol, also known as hydrocortisone, accounts for 95% of the glucocorticoids released from the adrenal cortex

Glucocorticoids
- Examples: Cortisol, Cortisone, Prednisone, Prednisolone, Methylprednisolone, Dexamethasone, Betamethasone, Triamcinolone, and Beclometasone
- Potency, duration of effect, and the overlapping mineralocorticoid potency vary between each drug
- Cortisol is the standard of comparison and hydrocortisone is the name used for pharmaceutical preparations of cortisol
- In comparison, hydrocortisone’s glucocorticoid and mineralocorticoid potency is equal and has a short duration of action, while dexamethasone has only glucocorticoid properties with no mineralocorticoid involvement and a long duration of action

Etomidate and Corticosteroid Administration
- The idea of corticosteroid supplementation after Etomidate use has been proposed to combat the adrenal insufficiency produced from its use
- Payen and colleagues study: Concluded critically ill patients without septic shock do not benefit from hydrocortisone administration and replacement doses are not required after a single dose of Etomidate
- Dr. Marik and Dr. Dmello: Agreed with Payen et al. and advised against the use of routine steroid supplementation

Etomidate and Critically Ill Patients
- The dispute over Etomidate use in critically ill patients has been a topic of debate for years due to the acute adrenal insufficiency
- Such adrenal insufficiency is hypothesized to be associated with higher rates of mortality
- Sunshine and colleagues study: Concluded the relative risk of death among the Etomidate recipients was higher than that of subjects given an alternative agent
Etomidate and Critically Ill Patients

- Van Den Heuvel and associates review: All three meta-analyses concluded findings of adrenal insufficiency and an increase in mortality
- Dr. Brian Fengler review: His summarized research indicated an association between a single induction dose of Etomidate in critically ill septic patient and sustained suppression of the adrenal axis with an increase in mortality
- Dr. Dean’s letter to the editor: Concluded Etomidate no longer has a role as the induction agent of choice in patients with septic shock

Recommendations

- It is essential for anesthesia providers to consider evidence-based recommendations to prevent potential adrenal insufficiency and increased mortality with Etomidate use
- Lack of abundant studies indicating a potential benefit of corticosteroids use
- Many studies advise against the use of Etomidate in critically ill individuals
- Studies specifically linking the cause and effect of Etomidate on mortality are needed
- Several studies suggest practitioners to seek out alternative induction techniques

Conclusion

- Additional large, randomized controlled studies are needed to provide a definite conclusion
- The majority of recent research indicates corticosteroids will not aid in preventing adrenal insufficiency and anesthesia providers should consider completely eradicating the use of Etomidate in critically ill individuals
- In the aforementioned case study, Etomidate or corticosteroids were not used for these reasons

References


References


References

Thank You
Are There Any Questions?