

Summary

Etomidate is an imidazole hypnotic agent characterized by a rapid onset of general anesthesia of short duration. In doses less than 0.25 mg/kg, etomidate has minimal effects on hemodynamic parameters, minimal respiratory depression, and very favorable effects on cerebral perfusion and the cerebral oxygen supply–demand ratio. For these reasons, etomidate is often the induction agent of choice in traumatized patients, especially those in shock, with unstable cardiopulmonary status, with multiple trauma, and/or with severe head injury, and in elderly patients with coexisting cardiovascular disease. Because of the risk of aspiration and apnea associated with induction of general anesthesia in the prehospital setting, a definitive airway is obtained routinely when administering etomidate, often aided by the use of neuromuscular relaxants.

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Perioperative Use of Etomidate for Trauma Patients

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Learning Objectives

1. To review the pharmacology of etomidate
2. To discuss the therapeutic uses of etomidate in the trauma patient

Case Presentation

A male driver of a motor vehicle is brought to the emergency department by air ambulance following an auto crash. The vehicle struck a tree head on, with the drive train being displaced into the passenger compartment. Witnesses stated that the driver was initially unconscious, regaining consciousness after several minutes, but was disoriented and uncooperative. The driver was wearing safety restraints and required 20 minutes for extrication.

In the emergency department, vital signs were a pulse of 110 beats per minute with a blood pressure of 100/80 mm Hg and a tissue oxygen saturation of 95%. The victim vocalizes and withdraws to painful stimuli, is uncooperative, opens his eyes randomly, and ventilates spontaneously. Examination reveals a fracture of the right tibia and fibula and a diagonal abrasion and contusion across the chest and abdomen. Chest film indicates two fractured ribs on the left and a widened mediastinum. Examination of the cervical spine is difficult due to lack of cooperation, and cervical spine films are inadequate to rule out cervical spine injury. Computerized tomography of the abdomen, cervical spine, and head are planned, followed by angiography of the thoracic aorta.

Comment

In view of the patient's neurologic status and inability to cooperate, elective intubation and general anesthesia will facilitate these procedures. Goals for induction of anesthesia for this patient include rapidly securing an airway to protect against aspiration and maintaining a stable blood pressure. This patient may be hypovolemic from hemorrhage and may

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manifest exaggerated hemodynamic responses to anesthetic agents. He may have a diminished myocardial reserve due to myocardial contusion as well. Cerebral perfusion pressure (CPP) must be maintained, as there may be cerebral ischemia, yet hypertension must be avoided to minimize the risk of additional intracerebral hemorrhage or hemorrhage from other injury. Finally, in the event that radiologic evaluation reveals no injuries requiring immediate surgical correction, it may be beneficial for the patient to be allowed to awaken and undergo serial neurologic assessments.

Etomidate (Amidate, Abbott Laboratories) is an anesthetic induction agent that offers many desirable qualities without significant untoward hemodynamic effects for this patient.

Background

Etomidate was first used clinically in 1973 but did not see widespread clinical use until the early 1980s. It was marketed as an alternative induction agent to thiopental. In particular because of its more than 10-fold increase in potency compared with thiopental (0.2–0.6 mg/kg for etomidate versus 3–6 mg/kg for thiopental)^{1,2} and relative lack of hemodynamic side effects, it was advocated for patients with cardiovascular compromise from underlying cardiac disease or for patients thought to be hemodynamically unstable from hypovolemia or hemorrhage. These beneficial effects would obviate some deleterious effects blamed on thiopental in the classic description of the care of injured soldiers at Pearl Harbor during World War II.³

Etomidate has also been used successfully for the treatment of seizures. Animal experiments have demonstrated its abortive effects on electrically and chemically induced convulsions. Although etomidate seemed to be well suited for use as an induction agent in the trauma patient, many practitioners continued to prefer ketamine for traumatized patients because of its positive effects on cardiac function, blood pressure, and heart rate through its sympathomimetic properties.^{4,5} Although both direct and indirect inotropic effects of ketamine have also been demonstrated in laboratory animals, these effects are seldom seen in patients, as those who are injured severely enough to be catecholamine depleted and demonstrate these negative cardiac effects are in such poor condition that anesthetic induction agents are usually deemed unnecessary and are rarely administered.^{6,7}

Etomidate has become popular for the induction of anesthesia in patients with cardiovascular compromise or suspected hypovolemia for elective and emergent surgery. It has also achieved acceptance as an alternative to thiopental for induction of anesthesia in the patient with neurotrauma and for intraoperative suppression of electroencephalographic (EEG) activity during aneurysm clipping, as it offers some measure of cerebral protection yet does not cause hypotension and decreased CPP. Lastly, etomidate, because of its associated hemodynamic stability, relative lack of respiratory depression, and brief duration of action, has also achieved popularity as a general anesthetic for procedures such as rapid-sequence intubation or cardioversion.^{8–12}

Physical Properties

Etomidate ([R]-[+]-ethyl-1-[1-phenylethyl]-1H-imidazole-5-carboxylate) is available as a 2-mg/ml solution in a 35% propylene glycol solution for use in the United States; other formulations are available or under investigation for use in

other countries.^{1,13} This solution is supplied in 10- and 20-ml ampules as well as 20-cc needle and needleless prepared syringes. It is stable at temperatures between 13°C and 30°C for storage.² In contrast to other induction agents, which are supplied as the racemic mixture, only the active (+) isomer of etomidate is supplied.¹

Pharmacokinetics

Etomidate has a volume of distribution similar to that for thiopental but a much more rapid clearance. This, combined with a hepatic extraction ratio of 0.90 (compared with a ratio of 0.15 for thiopental), results in more rapid elimination of the drug from the body, although redistribution remains the primary mechanism for termination of clinical effect. The elimination half-life for etomidate is approximately 3 hours, compared with 12 hours for thiopental.¹ This provides an added margin of safety over thiopental should large or repeated doses be administered in a single patient, which causes elimination to play a role in awakening (Table 1). Hemorrhagic shock produced minimal changes in the pharmacokinetics and no change in the pharmacodynamics of etomidate in swine.¹⁴ Thus, unlike other sedative hypnotics and opioids, minimal adjustment in the dose of etomidate is required to achieve the same drug effect during hemorrhagic shock.^{15–18}

Table 1. A Comparison of Pharmacokinetic Properties of Induction Agents

Agent	Vdss (L/kg)	Clearance (mL/kg)	Half-Life (hr)	Hepatic Extraction Ratio
Thiopental	2.34	3.4	12.0	0.15
Ketamine	3.10	19.1	3.1	~1.0
Midazolam	1.09	7.5	2.7	0.51
Propofol	2.83	59.4	0.9	~1.0
Etomidate	2.52	17.9	2.9	0.90

Data assembled from Fragen and Avram.¹
Vdss, volume of distribution.

Physiologic Effects

Central Nervous System (CNS). Etomidate, like thiopental, is thought to act at the gamma-aminobutyric acid (GABA) receptor, although it appears to increase the number of available receptors by displacing endogenous inhibitors rather than increasing GABA receptor affinity, as is the case of barbiturates. It was recently shown that the beta2 subunit contributes to the sedative properties of etomidate, whereas the beta3 subunit is responsible for its general anesthetic properties.¹⁹ GABA(A) receptors may possess two types of etomidate sites: high-affinity GABA-modulating sites and low-affinity channel-activating sites.²⁰

Etomidate produces effects similar to those of barbiturate administration with increased amplitude and slowing of frequency, followed by burst suppression at higher doses and flattening of the EEG pattern.²¹ Myoclonic activity is common with etomidate administration, although concomitant EEG

changes consistent with seizure activity are not seen in these patients.²² Rarely, however, etomidate has been reported to unmask or enhance seizure activity in susceptible subjects; this effect is unrelated to the myoclonic activity more commonly seen.²³

Beneficial CNS effects, particularly in the head-injured patient, include a reduction in cerebral blood flow, cerebral metabolic rate for oxygen consumption (CMRO₂) and intracranial pressure (ICP).^{24,25} Etomidate, in contrast to thiopental, provides these effects without a decrease in systemic blood pressure such that the CPP is better maintained (Table 2).²⁶ In doses that achieve burst suppression, etomidate has been shown to achieve a 50% decrease in ICP in patients with intracranial mass lesions without significant changes in mean arterial pressure (MAP), CPP, or heart rate (HR).²⁷ Because of its ability to maintain CPP yet provide burst suppression, it has become the agent of choice for temporary arterial occlusion during intracranial aneurysm clipping.²⁸

Although etomidate has been shown to depress CMRO₂, animal data suggest that this cerebral protection may not be uniform throughout the brain. In a dog model, etomidate failed to suppress brainstem auditory-evoked response (BAERs), suggesting etomidate may not protect the brainstem well during ischemia.²⁹ Likewise, in a rat model of forebrain ischemia, there was only limited cerebral protection demonstrated with either isoflurane, thiopental, or etomidate.^{30,31} However, etomidate may offer potential as the induction agent of choice for these procedures, because it does not suppress BAERs and is less likely to suppress transcranial motor-evoked response (tc-MERs) than thiopental or propofol.^{32,33}

Cardiovascular. Minimal negative or absent cardiovascular effects are highly desirable in the patient with cardiovascular compromise or hypovolemia. Etomidate causes, at most, transient slight decreases in HR, systemic blood pressure, and systemic vascular resistance. A lack of change in

dP/dT and minimal change in cardiac function measured by systolic shortening, left ventricular force, and fractional shortening compared with other reduction agents such as etiopental and propofol have been reported.^{34,35} Using echocardiography, Gauss et al demonstrated that etomidate has no effect on cardiac inotropy or afterload, whereas thiopental had predominantly negative inotropic effects and propofol had both negative inotropic and negative effects on afterload.³⁶ Etomidate has also been shown to increase coronary blood flow and decrease oxygen consumption (MVO₂).³⁷ A negative inotropic effect of etomidate has been demonstrated, which is likely due to altered intracellular calcium influx.³⁸ However, this was in papillary muscle preparations and at concentrations well in excess of clinically relevant doses.³⁹ The lack of cardiovascular effects is thought to be a result of etomidate's lack of effect on the sympathetic nervous system and autonomic reflexes compared with other agents.⁴⁰⁻⁴² Etomidate exhibits structural similarities to alpha2-adrenoceptor agonists such as dexmedetomidine and has been shown in an animal model to cause an alpha2B-receptor-mediated increase in blood pressure.⁴³ This effect of etomidate may contribute to the cardiovascular stability of patients after induction of anesthesia with etomidate. In addition, etomidate, in contrast to propofol, had no effect on the threshold for epinephrine-induced arrhythmias, which may be important in patients who have high levels of circulating catecholamines.⁴⁴ These minimal deleterious effects on the cardiovascular system make this agent desirable for the traumatized patient as well as the patient with cardiac compromise (Table 3).

Respiratory. Etomidate, although a respiratory depressant in a dose-related fashion, has been shown to depress ventilation less than equipotent doses of barbiturates or propofol. This makes etomidate useful for brief procedures during which spontaneous ventilation is desired. There is also little effect on bronchomotor tone; however, the drug only rarely causes allergic reactions or bronchospasm.

Other. Etomidate has been shown to be suitable for induction of anesthesia in patients with open eye injuries, as it diminishes intraocular pressure in a similar fashion to all other commonly used induction agents, with the exception of ketamine.⁴⁵

Gill and Scott⁴⁶ demonstrated that, compared with thiopental and propofol, the onset of neuromuscular blockade was significantly shortened with etomidate, which was most likely a result of the favorable hemodynamic profile, which preserved skeletal muscle blood flow.

As with all agents, there are side effects with etomidate; however, they are relatively minor. The most significant is the ability of etomidate to suppress adrenal steroidogenesis probably by

Table 2. A Comparison of Cerebrovascular Effects of Induction Agents

Agent	Cerebral Blood Flow	Intracranial Pressure	Cerebral Perfusion Pressure	Cerebral Metabolic Rate of O ₂
Thiopental	↓↓	↓↓	↓↓	↓↓
Ketamine	↑↑	↑	↑	↑
Midazolam	↓	↓	↓	↓
Propofol	↓↓	↓↓	↓↓	↓↓
Etomidate	↓↓	↓↓	-	↓↓

Table 3. A Comparison of Cardiovascular Properties of Induction Agents

Agent	Mean Arterial Pressure	Heart Rate	Systemic Vascular Resistance	Venodilation	Cardiac Output	Contractility
Thiopental	↓	↑	-↑	↑	↓	↓
Ketamine	↑↑	↑↑	↑	-	↑	↓ or ↑*
Midazolam	-↓	-↑	-↓	↑	-↓	↓
Propofol	↓	↑	↓	↑	-	↓
Etomidate	-	-	-	-	-	-

*Dependent on intrinsic catecholamine levels.

inhibiting the 11-beta-hydroxylase pathway, which lasts for 6 to 8 hours after administration.⁴⁷ While this was of great concern and led to the elimination of etomidate for use as an infusion for long-term sedation of critical care patients, this is not a concern for the single-bolus administration of etomidate for anesthetic induction or deep sedation for brief procedures.⁴⁸ In a randomized, controlled trial of consecutive patients presenting to the emergency department requiring intubation, Schenarts et al studied adrenocortical function after induction with etomidate or midazolam.⁴⁹ Serum cortisol response to exogenous cosyntropin (cosyntropin stimulation test [CST]) was measured at 4, 12, and 24 hours post-induction. Although the 4-hour CST results were significantly different between study groups, with a normal response in 100% of control patients versus 30% of etomidate patients, the 12- and 24-hour CSTs did not differ significantly between groups. Measured cortisol levels of patients with abnormal CSTs remained within normal laboratory reference ranges. The authors concluded that adrenocortical dysfunction appears to resolve within 12 hours of a single bolus dose of 0.3 mg/kg etomidate.⁴⁹ Crozier et al⁵⁰ demonstrated that the stress response during cardiac surgery overcame the block of cortisol synthesis through increased secretion of adrenocorticotrophic hormone (ACTH).

Other side effects include venous irritation, nausea and vomiting, and excitatory effects, including myoclonic movements that may distress the uninitiated observer but are harmless to the patient.²² These are of little concern in the trauma and critical care patient populations.

Current Status

Etomidate has had a long and consistent use as an alternative to thiopental for the induction of anesthesia and for sedation for brief procedures. The growth of neuromonitoring, ongoing research into agents for cerebral protection, and the search for ways to provide a stable anesthetic induction and surgical course for cardiac surgical patients yet avoid the prolonged postoperative intubation and ventilation necessary for high-dose narcotic techniques have caused a renewed interest in the role of etomidate as an induction agent. Many of the concerns for neurosurgical patients, cardiac patients, and patients with an uncertain volume status or known hypovolemia also apply to the trauma patient.

With increasing involvement of anesthesia providers as part of a trauma team that provides care to trauma victims as they arrive in the emergency department, the need for an induction agent that provides cerebral protection and cardiovascular stability becomes essential. Because etomidate is associated with hemodynamic stability and a low incidence of hypotension, it has become widely accepted as an induction agent for prehospital and emergency department rapid-sequence intubation.

The increasing use of general anesthesia to facilitate diagnostic and therapeutic procedures such as fracture or dislocation reduction, computed tomography scanning, intracranial monitoring, transesophageal echocardiography, and angiography in patients whose extent of injury is unknown makes etomidate an ideal choice.

In the past, patients have arrived at the operating room for surgical procedures with their workup and resuscitation fairly complete. This allowed the use of thiopental in patients with head injury who had been resuscitated, and ketamine was

suitable for nearly all other patients, as it protected against hemodynamic instability in the unsuspected hypovolemic or incompletely resuscitated patient. Although the adrenal suppression is a matter of concern, it is apparently short-lived and incomplete. Data in cardiac surgery patients indicate that, while adrenal suppression does occur, contrary to previous data, increased ACTH levels appear to overcome this suppression in this patient population and normal cortical levels are maintained during their surgical course. Adrenocortical dysfunction appears to resolve within 12 hours of a single bolus dose of 0.3 mg/kg etomidate, and measured cortisol levels of patients with abnormal cosyntropin stimulation test remain within normal lab values. Furthermore, in trauma patients with spinal cord injury, exogenous steroids may be administered as part of their treatment.

In conclusion, etomidate offers cardiovascular stability and cerebral protection with no significant negative side effects in the management of the trauma patient.

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Etomidate as an Induction Agent in Trauma Anesthesia

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Learning Objectives

1. To review the pharmacokinetics of etomidate
2. To describe the side effect profile of etomidate
3. To evaluate the use of etomidate in the trauma patient

Etomidate is an ultra-short-acting induction agent. It is a carboxylated imidazole-derived nonbarbiturate, nonnarcotic, hypnotic agent mainly used for induction of general anesthesia. It acts by modulating and mimicking γ -aminobutyric acid type A receptors. Synthesized in 1964, it was introduced as an intravenous anesthetic agent in 1972.^{1,2}

It was hailed early as an ideal agent because of maintenance of hemodynamic stability even in patients with marked hypovolemia, minimal respiratory depression, cerebral protection, and rapid recovery. However, by the early 1980s, reports indicated that etomidate might inhibit steroid synthesis, thus increasing mortality in patients sedated with the drug for long periods in intensive care units.^{3,4} Another study suggested that even a single induction dose might be unsafe.⁵ Propofol became the preferred induction agent, and the use of etomidate fell dramatically in the United States.

Now, more than 30 years later, it is appropriate to reevaluate this important drug and identify means whereby the beneficial effects may be put to maximum use while adverse actions may be minimized. It is perhaps not surprising that most studies over the past 10 years have appeared in the British and Canadian literature.

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