Sedative Induction Agents

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INTRODUCTION

Agents used to sedate, or “induce,” patients for intubation during rapid sequence intubation (RSI) are properly called sedative induction agents because induction of general anesthesia is at the extreme of the spectrum of their sedative actions. In this chapter, we refer to this family of drugs as “induction agents.” The ideal induction agent would smoothly and quickly render the patient unconscious, unresponsive, and amnestic in one arm/heart/brain circulation time. Such an agent would also provide analgesia, maintain stable cerebral perfusion pressure and cardiovascular hemodynamics, be immediately reversible, and have few, if any, adverse side effects. Unfortunately, such an induction agent does not exist. Most induction agents meet the first criterion because they are highly lipophilic and, therefore, have a rapid onset within 15 to 30 seconds of intravenous (IV) administration. Their clinical effect is likewise terminated quickly as the drug rapidly redistributes to less well-perfused tissues. All induction agents have the potential to cause myocardial depression and subsequent hypotension. These effects depend on the particular drug; the patient’s underlying physiologic condition; and the dose, concentration, and speed of injection of the drug. The faster the drug is administered (IV push), the larger the concentration of drug that saturates those organs with the greatest blood flow (i.e., brain and heart), and the more pronounced the effect. Because RSI requires rapid administration of a preselected dose of the induction agent, the choice of drug and the dose must be individualized to capitalize on desired effects, while minimizing those that might adversely affect the patient. Some patients are so unstable that the primary goal is to produce amnesia rather than anesthesia because to produce the latter might lead to severe hypotension and organ hypoperfusion.

The induction agents include ultra–short-acting barbiturates: thiopental (Pentothal) and methohexital (Brevital); benzodiazepines: principally midazolam (Versed); and miscellaneous agents: etomidate (Amidate), ketamine (Ketalar), and propofol (Diprivan). Thiopental (Pentothal) is no longer available for clinical use in the United States, Canada, or the rest of the developed world. Other agents, such as the opioid analgesic fentanyl (Sublimaze), can function as anesthetic induction agents when used in large doses (e.g., for fentanyl 30 \( \mu \)g [0.03 mg] per kg); however, they are rarely, if ever, used for that purpose during emergency intubation, and so are not discussed here.

General anesthetic agents act through two principal mechanisms: (1) an increase in inhibition through \( \gamma \)-aminobutyric acid. A receptors (e.g., benzodiazepines, barbiturates, propofol, etomidate, isoflurane, enflurane, and halothane), and (2) a decreased excitation through \( N \)-methyl-D-aspartate (NMDA) receptors (e.g., ketamine, nitrous oxide, and xenon). Dexmedetomidine is a relatively selective \( \alpha_2 \)-adrenergic agonist (like clonidine) with sedative properties, and is used in the operating room and ICU settings for procedural sedation (e.g., awake intubation), as a component of balanced anesthesia, and for the sedation of intubated patients. Dexmedetomidine is not an induction agent and its role in emergency medicine for procedural sedation is yet to be determined.

The IV induction agents discussed in this chapter share important pharmacokinetic characteristics. Induction agents are highly lipophilic and because the brain is a highly perfused, lipid dense organ, a standard induction dose of each agent in a euvoelastic, normotensive patient will produce induction within 30 seconds. The blood–brain barrier is freely permeable to medications used to induce anesthesia. The observed clinical duration of each drug is measured in minutes because of the drug’s distribution half-life (\( t_{1/2}\alpha \)), characterized by distribution of the drug from the central circulation to well-perfused tissues, such as brain. The redistribution of the drug from brain to fat and muscle terminates its CNS effects. The elimination half-life (\( t_{1/2}\beta \), usually measured in hours) is characterized by each drug’s reentry from fat and lean muscle into plasma down a concentration gradient leading to hepatic metabolism and renal excretion. Generally, it requires four to five elimination half-lives to completely clear the drug from the body.

The dosing of induction agents in nonobese adults should be based on ideal body weight (IBW) in kilograms. In clinical practice, the actual body weight is a reasonable enough approximation to IBW for the purposes of dosing these agents.
For obese patients, the situation is more complicated. The high lipophilicity of the induction agents combined with the increased volume of distribution (Vd) of these drugs in obesity argues for actual body weight dosing (see Chapter 39). Opposing this, however, is the significant cardiovascular depression that would occur if such a large quantity of drug is injected as a single bolus. Balancing these two considerations, and given the paucity of actual pharmacokinetic studies in obese patients, the best approach is to use Lean Body Weight (LBW) for dosing of most induction agents, decreasing to IBW if the patient is hemodynamically compromised, or for drugs with significant hemodynamic depression, such as propofol. LBW is obtained by adding 0.3 of the patient’s excess weight (actual body weight minus IBW) to the IBW, and using the sum as the dosing weight. This is in contrast to succinylcholine, which is dosed at total body weight. Drug dosing for obese patients is discussed in Chapter 39.

Aging affects the pharmacokinetics of induction agents. In elderly patients, lean body mass and total body water decrease while total body fat increases, resulting in an increased volume of distribution, an increase in t1/2b and an increased duration of drug effect. In addition, the elderly are more sensitive to the hemodynamic and respiratory depressant effects of these agents, and the induction doses should be reduced to approximately one-half to three-fourths of the dose used in their healthy, younger counterparts.

**ETOMIDATE**

<table>
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<tr>
<th>Etomidate (Amidate)</th>
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<tr>
<td>Usual emergency induction dose (mg/kg)</td>
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**Clinical Pharmacology**

Etomidate is an imidazole derivative that is primarily a hypnotic and has no analgesic activity. With the exception of ketamine, etomidate is the most hemodynamically stable of the currently available induction agents. It exerts its effect by enhancing GABA activity at the GABA–receptor complex, inhibiting excitatory stimuli. Etomidate attenuates underlying elevated intracranial pressure (ICP) by decreasing cerebral blood flow (CBF) and cerebral metabolic oxygen demand (CMRO2). Its hemodynamic stability preserves cerebral perfusion pressure. Etomidate may not be the most cerebroprotective of the various available induction agents (that attribute probably resides with the barbiturates), but its hemodynamic stability and favorable CNS effects make it an excellent choice for patients with elevated ICP.

Etomidate does not release histamine and is safe for use in patients with reactive airways disease. However, it lacks the direct bronchodilatory properties of ketamine, which may be a preferable agent in these patients.

**Indications and Contraindications**

Etomidate has become the induction agent of choice for most emergent RSIs because of its rapid onset, its hemodynamic stability, its positive effect on CMRO2 and cerebral perfusion pressure, and its rapid recovery. As with any induction agent, dosage should be adjusted in hemodynamically compromised patients. Etomidate is a U.S. Food and Drug Administration (FDA) pregnancy category C drug.

Etomidate is not FDA approved for use in children, but many series report safe and effective use in pediatric patients.
Dosage and Clinical Use

In euvoletic and hemodynamically stable patients, the normal induction dose of etomidate is 0.3 mg per kg IV push. In compromised patients, the dose should be reduced commensurate with the patient’s clinical status; reduction to 0.2 mg per kg is usually sufficient. In morbidly obese patients, the induction dose should be based on lean body weight, by using IBW and adding a correction of 30% of the weight.

Adverse Effects

Pain on injection is common because of the diluent (propylene glycol) and can be somewhat mitigated by having a fast-flowing IV solution running in a large vein. Myoclonic movement during induction is common and has been confused with seizure activity. It is of no clinical consequence and generally terminates promptly as the neuromuscular blocking agent takes effect.

The most significant and controversial side effect of etomidate is its reversible blockade of 11β-hydroxylase, which decreases both serum cortisol and aldosterone levels. This side effect has been more common with continuous infusions of etomidate in the ICU setting than with a single-dose injection used for emergency RSI. The risks and benefits of the use of etomidate in patients with sepsis are discussed in detail in the “Evidence” section at the end of the chapter.

### KETAMINE

<table>
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<th>Ketamine (Ketalar)</th>
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<td><strong>Usual emergency induction dose (mg/kg)</strong></td>
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<td>1.5</td>
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Clinical Pharmacology

Ketamine is a phencyclidine derivative that provides significant analgesia, anesthesia, and amnesia, with minimal effect on respiratory drive. The amnestic effect is not as pronounced as that seen with the benzodiazepines. Ketamine is believed to interact with the NMDA receptors at the GABA–receptor complex, promoting neuroinhibition and subsequent anesthesia. Action on opioid receptors accounts for its profound analgesic effect. Ketamine releases catecholamines, stimulates the sympathetic nervous system, and therefore augments heart rate and BP in those patients who are not catecholamine-depleted secondary to the demands of their underlying disease. Furthermore, increases in mean arterial pressure may offset any rise in ICP, resulting in a relatively stable cerebral perfusion pressure. This is discussed in detail in the “Evidence” section. In addition to its catecholamine-releasing effect, ketamine directly relaxes bronchial smooth muscle, producing bronchodilation. Ketamine is primarily metabolized in the liver, producing one active metabolite, norketamine, which is metabolized and excreted in the urine.

Indications and Contraindications

Ketamine is the induction agent of choice for patients with reactive airways disease who require tracheal intubation. Ketamine is an excellent induction agent for patients who are hypovolemic, hypotensive, or hemodynamically unstable, including those with sepsis. In normotensive or hypertensive patients with ischemic heart disease, catecholamine release may adversely increase
myocardial oxygen demand, but it is unlikely that this effect is detrimental in patients with significant hypotension, in whom additional catecholamine release may support the blood pressure. Ketamine’s preservation of upper airway reflexes makes it appealing for awake laryngoscopy and intubation in the difficult airway patient where the dose is titrated to effect. The effects of ketamine on ICP will be discussed in the “Evidence” section. The pregnancy category of ketamine has not been established by the FDA so it is not currently recommended for use in pregnant women.

**Dosage and Clinical Use**

The induction dose of ketamine for RSI is 1 to 2 mg per kg IV. In patients who are catecholamine depleted, doses >1.5 mg per kg IV may cause myocardial depression and exacerbate hypotension. For sedation, ketamine is titrated to effect beginning with 0.2 mg per kg IV. Because of its generalized stimulating effects, ketamine enhances laryngeal reflexes and increases pharyngeal and bronchial secretions. These secretions may uncommonly precipitate laryngospasm, and may interfere with upper airway examination during awake intubation, but are not an issue during RSI. Atropine 0.01 mg per kg IV or glycopyrrolate (Robinul) 0.01 mg per kg IV may be administered 15 to 20 minutes before ketamine to promote a drying effect for awake intubation, when feasible. Ketamine is available in three separate concentrations: 10, 50, and 100 mg per ml. Care should be taken to ensure that only one concentration is stored in the emergency department.

**Adverse Effects**

Hallucinations may occur on emergence from ketamine and are more common in the adult than in the child. They may be attenuated by the concomitant or subsequent administration of a benzodiazepine, if desired. Such emergence reactions occur infrequently in the emergency department as most patients are subsequently sedated with either a benzodiazepine, or with propofol, after the airway has been secured.

**PROPOFOL**

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<th>Propofol (Diprivan)</th>
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<tr>
<td>Usual emergency induction dose (mg/kg)</td>
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<td>1.5</td>
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**Clinical Pharmacology**

Propofol is an alkylphenol derivative (i.e., an alcohol) with hypnotic properties. It is highly lipid soluble. Propofol enhances GABA activity at the GABA–receptor complex. It decreases CMRO$_2$ and ICP. Propofol does not cause histamine release. Propofol causes a reduction in BP through vasodilation and direct myocardial depression. The ensuing hypotension, or the resultant decrease in cerebral perfusion pressure, may be detrimental in a compromised patient. The manufacturer recommends that rapid bolus dosing (either single or repeated) be avoided in patients who are elderly, debilitated, or ASA Class III or IV in order to minimize undesirable cardiovascular depression, including hypotension. It must be used cautiously for emergency RSI in hemodynamically unstable patients.
### Indications and Contraindications

Propofol is an excellent induction agent in a stable patient. Its adverse potential for hypotension and reduction in cerebral perfusion pressure limits its role as an induction agent in emergent RSI. Propofol has been used successfully as an induction agent during tracheal intubation for reactive airways disease. There are no absolute contraindications to the use of propofol. Propofol is delivered as an emulsion in soybean oil and lecithin. Patients who are allergic to eggs generally react to the ovalbumin and not to lecithin, so propofol is not contraindicated in patients with egg allergy. Propofol is a pregnancy category B drug, and has become the induction agent of choice in pregnant patients.

### Dosage and Clinical Use

The induction dose of propofol is 1.5 mg per kg IV in a euvoletic, normotensive patient. Because of its predictable tendency to reduce mean arterial BP, doses are reduced by 1/3 to 1/2 when propofol is given as an induction agent for emergency RSI in compromised or elderly patients.

### Adverse Effects

Propofol causes pain on injection, which can be attenuated by injecting the medication through a rapidly running IV in a large vein (e.g., antecubital). Premedication of the vein with lidocaine (2 to 3 ml of 1% lidocaine) will also minimize the pain of injection. Propofol and lidocaine are compatible in the same syringe and can be mixed in a 10:1 ratio (10 ml of propofol to 1 ml of 1% lidocaine). Propofol can cause mild clonus to a greater degree than thiopental, but less than etomidate or methohexital. Venous thrombophlebitis at the injection site may occasionally occur.

### Methohexital

#### Clinical Pharmacology

Thiopental was once the prototypical barbiturate used for anesthetic induction. In January 2011, however, thiopental was removed from clinical use in the United States, Canada, the United Kingdom, Australia, and New Zealand, citing concerns from the manufacturer that clinical supplies could be used in lethal injection. Methohexital is a close relative of thiopental and remains in clinical use. Both are ultra–short-acting CNS depressants that induce hypnosis (sleep) but not analgesia. Recovery after a small dose is rapid with some somnolence and retrograde amnesia. Repeated IV doses lead to prolonged anesthesia because fatty tissues act as a reservoir. Methohexital is two to three times more potent than thiopental, 1.5 mg of methohexital being equal to 4 mg of thiopental. The $t_{1/2B}$ for methohexital is shorter than that for thiopental.
At low doses, ultra–short-acting barbiturates decrease GABA dissociation from its receptor, which enhances GABA’s neuroinhibitory activity. At higher doses, they can directly stimulate the GABA receptor itself. Barbiturates are cerebroprotective, causing a dose-dependent decrease in cerebral metabolic oxygen consumption and a parallel decrease in CBF and ICP, provided cerebral perfusion pressure is maintained.

Thiopental and methohexital are largely degraded in the liver. Neither have active metabolites.

**Indications and Contraindications**

Thiopental was widely used as an induction agent in the past, but it has largely been supplanted by etomidate and propofol. It is currently unavailable for clinical use. Methohexital is primarily used for procedural sedation and is rarely used for induction.

**Dosage and Clinical Use**

The dosing of ultra–short-acting barbiturates depends on the hemodynamic status of the patient and the concomitant use of other agents in RSI. The recommended induction dose of methohexital in the euvoletic, normotensive patient is 1.5 mg per kg IV. For procedural sedation or an assisted laryngoscopy, half this dose should be used.

The ultra–short-acting barbiturates should be avoided entirely in frankly hypotensive patients for whom other drugs, such as etomidate or ketamine, may preserve greater hemodynamic stability. With the widespread adoption of etomidate, which has significant cardiovascular stability, the ultra–short-acting barbiturates are rarely used as induction agents for emergent RSI.

**Adverse Effects**

The principal side effects of barbiturates include central respiratory depression, venodilation, and myocardial depression. Barbiturates cause a dose-related release of histamine that rarely is clinically significant, but may cause or exacerbate bronchospasm in patients with reactive airways disease. Ketamine is the preferred induction agent for patients with reactive airways disease. Methohexital causes more excitatory phenomena (twitching and hiccups) than thiopental.

Inadvertent intra-arterial injection or subcutaneous extravasation of ultra–short-acting barbiturates can result in chemical endarteritis and distal thrombosis, ischemia, and tissue necrosis because they have a highly alkaline pH (>10). If extravasation occurs, 40 to 80 mg of papaverine (Cerespan) in 20 ml normal saline or 10 ml of 1% lidocaine (Xylocaine) should be injected intra-arterially proximal to the site to inhibit smooth muscle spasm. Consider local infiltration of an α-adrenergic blocking agent, such as phentolamine, into the vasospastic area.

**BENZODIAZEPINES**

<table>
<thead>
<tr>
<th>Short-Acting Benzodiazepines</th>
<th>Usual emergency induction dose (mg/kg)</th>
<th>Onset (s)</th>
<th>$t_{1/2}^{\alpha}$ (min)</th>
<th>Duration (min)</th>
<th>$t_{1/2}^{\beta}$ (h)</th>
</tr>
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<tbody>
<tr>
<td>Midazolam</td>
<td>0.2–0.3</td>
<td>60–90</td>
<td>7–15</td>
<td>15–30</td>
<td>2–6</td>
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Versed
Clinical Pharmacology

Although chemically distinct from the barbiturates, the benzodiazepines also exert their effects through the GABA–receptor complex. Benzodiazepines specifically stimulate the benzodiazepine receptor, which in turn modulates GABA, the primary neuroinhibitory transmitter. The benzodiazepines provide amnesia, anxiolysis, central muscle relaxation, sedation, anticonvulsant effects, and hypnosis. Although the benzodiazepines generally have similar pharmacologic profiles, they differ in selectivity, which makes their clinical usefulness variable. The benzodiazepines have potent, dose-related amnestic properties, perhaps their greatest asset for emergency indications. The three benzodiazepines of interest for emergency applications are midazolam (Versed), diazepam (Valium), and lorazepam (Ativan). Of the three, midazolam is the most lipid soluble and is the only benzodiazepine suitable for use as an induction agent for emergent RSI. Midazolam rarely is used as an induction agent for emergent RSI, however, because its time to clinical effectiveness is much longer than is the case for any of the other commonly used induction agents. When IV midazolam is given as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when narcotic premedication has been used, and in 2 to 2.5 minutes without narcotic premedication. This slow onset of action is mitigated by the profound amnestic effects of midazolam. Its pharmacokinetic attributes, however, make it a poor induction agent, and it cannot be recommended for this purpose. Midazolam has one significant active metabolite, 1-hydroxy-midazolam, which may contribute to the net pharmacologic activity of midazolam. Clearance of midazolam is reduced in association with old age, congestive heart failure, and liver disease. The elimination half-life of midazolam ($t_{1/2}$) may be prolonged in renal impairment. The benzodiazepines do not release histamine, and allergic reactions are very rare.

Indications and Contraindications

The primary indications for benzodiazepines are to promote amnesia and sedation. In this regard, the benzodiazepines are unparalleled. Midazolam’s primary use in the emergency department and elsewhere in the hospital is for procedural sedation. Lorazepam is used primarily for treatment of seizures and alcohol withdrawal, and both agents are used for sedation and anxiolysis in a variety of settings, including postintubation.

Because of their dose-related reduction in systemic vascular resistance and direct myocardial depression, dosage must be adjusted in volume-depleted or hemodynamically compromised patients. Studies have shown that the correct induction dose of midazolam, 0.3 mg per kg, is rarely used. Even at this dose, midazolam is a poor induction agent for emergent RSI because of delay in onset of action and adverse hemodynamic effects.

All benzodiazepines are FDA pregnancy category D.

Dosage and Clinical Use

Although midazolam is occasionally used as an induction agent in the operating room, we do not recommend its use for emergent RSI. Even in the correct induction dose for hemodynamically stable patients of 0.2 to 0.3 mg per kg IV push, the onset is slow, and so the drug is not suited to emergency applications. Midazolam should be reserved for sedative applications, and its use in emergency RSI is not advised because superior agents are readily available. Similarly, diazepam and lorazepam are not recommended for emergent RSI because of their slow onset of action.

Adverse Effects

With the exception of midazolam, the benzodiazepines are insoluble in water and are usually in solution in propylene glycol. Unless injected into a large vein, pain and venous irritation on injection can be significant.
Is etomidate safe to use in septic patients? Etomidate has become the preferred agent for emergent RSI in North America and in much of the rest of the world because of its simple dosing strategies, reliable onset of action, and cardiovascular stability. The debate about the safety of etomidate in patients with sepsis has been raging for much of the last decade. The debate regarding the safety of etomidate in patients with sepsis has occurred within the larger discussion of critical illness relative corticosteroid insufficiency (CIRCI) and the role of corticosteroids in the management of critically ill patients. CIRCI, however, is more complicated than a simple reduction in circulating cortisol levels, and likely stems from a dysfunction at the level of the hypothalamic pituitary axis. Many of the features of CIRCI are still being identified, but likely include decreased production of corticotropin-releasing hormone, adrenocorticotropic hormone (ACTH), cortisol, and perhaps critically, dysfunction of the glucocorticoid receptors.

Confounding this is the inability to precisely characterize the nature and role of adrenal insufficiency in critical illness and how this may or may not relate to total cortisol levels or response to ACTH. The current consensus recommendations are to base decisions related to glucocorticoid administration on clinical evaluation and not on laboratory testing. A single dose of etomidate causes a reversible inhibition of adrenal hormone synthesis by blocking 11β-hydroxylase. It was for this reason that etomidate infusions ceased to be used for ICU sedation in the early 1980s. Following a single dose of etomidate, there is an immediate inhibition of adrenal hormone synthesis that lasts 12 to 24 hours, and may extend as long as 72 hours in some patients. What remains unclear is whether there are any significant clinical sequelae from the transient inhibition of adrenal hormonal synthesis.

For the most part, there is broad agreement that in patients without sepsis or sepsis-like syndromes, the advantages of etomidate significantly outweigh concerns about possible inhibition of adrenal hormone synthesis.

For patients with sepsis or with sepsis-like syndromes, there remains much debate as to the potential risks of etomidate. The literature is significantly divided. Much of the data has emerged from observational studies and post hoc analyses. There have been many review articles and several meta-analyses. However, very few patients have been enrolled in randomized controlled trials, and several studies used cortisol levels as the primary outcomes and did not address mortality or length of stay. In 2009, Jabre et al. published an RCT comparing 234 patients in the etomidate group and 235 in a ketamine group. Although the percentage of patients with adrenal insufficiency was significantly higher in the etomidate group, they found no serious adverse events with either study drug. The number of patients with sepsis as the final diagnosis was 41 in the etomidate group and 35 in the ketamine group. In August 2010, a comprehensive metanalysis concluded that although etomidate suppresses adrenal function transiently, there is no significant mortality effect based on the current data.

In November 2010, Tekwani et al. published an RCT comparing etomidate (n = 61) and midazolam (n = 59) as induction agents in patients with a primary infectious cause for their illness, with primary outcome measure of hospital length of stay and secondary outcomes of ICU length of stay, ventilator days, and mortality. They found no significant differences in their primary or secondary outcomes. To date, no study has been adequately powered to detect a small difference in mortality or in hospital, ICU, or ventilator length of stay.

The debate over the safety of etomidate in sepsis patients has expanded in recent years. There is recognition that some degree of adrenal insufficiency occurs in many patients with critical illness, and that measurement of total cortisol levels is likely oversimplifying the problem.

For the emergency physician who relies upon etomidate for the simple dosing regimen, rapid onset of action, and lack of cardiovascular compromise, even in patients who are hemodynamically unstable, there are three main choices in the patient with presumptive sepsis:
• Avoid etomidate use entirely in patients who are presumed to be septic. Some advocates of this approach emerged early in the debate, but as further data have emerged, the possible risk of etomidate use in septic patients appears to have been overstated and a clinical equipoise has developed. The risk of using etomidate must be balanced against the risk of an alternative agent. Only ketamine provides hemodynamic stability comparable with etomidate, and ketamine is not available in many settings where emergent intubation is performed.

• Routinely administer glucocorticoids to patients with septic shock who have received etomidate. The emerging recognition of the relationship between critical illness and adrenal insufficiency (CIRCI) has made this question both simpler and more complex. Studies of supplemental corticosteroids in patients with sepsis have had equivocal results. Although it has been posited that glucocorticoids should be given immediately after the administration of etomidate when the adrenal suppression is likely to be greatest, there is no evidence that this approach improves patient outcome. The current international consensus is that supplemental “glucocorticoids should be considered in the management of septic patients when they have responded poorly to fluid resuscitation and vasopressor agents.”

• Communicating clearly to critical care staff that the patient was given a dose of etomidate for induction. It is almost impossible to argue against this common sense approach.

• Which induction agents are the most hemodynamically stable when used for RSI? In RSI, a predetermined dose of an induction agent is given at the same time as a muscle relaxant. The physician makes his or her best estimation of the dose of induction agent required and the dose is not titrated. The physician aims to give a large enough dose of induction agent to prevent awareness, while minimizing the risk of hemodynamic collapse. Although virtually all induction agents could be used for RSI, not all are appropriate. We want to avoid both patient awareness and hemodynamic compromise. The ideal induction agent in RSI will have rapid and reliable onset and few adverse (particularly hemodynamic) effects.

  Etomidate results in the least variation in BP and heart rate when compared with the other agents used for rapid induction of anesthesia. This cardiovascular stability is seen in both children and adults, including the elderly. The drug is delivered to the CNS in a timely and dependable manner. It is for these reasons that etomidate remains the standard choice for RSI.

  Propofol is a very popular induction agent for elective procedures, when the induction dose is titrated against the patient response. It is a poor choice of induction agent for RSI in hemodynamically compromised patients, who run the risk of further hemodynamic deterioration coupled with awareness during intubation.

  Thiopental, for many years the staple induction agent for RSI, is no longer available for clinical use in North America, the United Kingdom, Europe, or Australasia (personal communication) following manufacturers concerns about thiopental use in lethal injection.

  Benzodiazepines are generally not suitable as induction agents in RSI. Midazolam is 95% protein bound. Both midazolam and lorazepam require closure of an imidazole ring to have enough lipid solubility to cross the blood–brain barrier, which take as long as 10 minutes. Some authors have referred to benzodiazepines as being “almost useless” for RSI.

  Ketamine offers several advantages as an induction agent in hemodynamically compromised patients. Ketamine is a sympathomimetic agent, increasing heart rate, arterial pressure, and cardiac output in animal models. Data on the use of ketamine as an induction agent in RSI are sparse. Conversely, there is significant clinical experience using ketamine for RSI, although much of it is in the resource-poor developing world or in warfare, neither of which lend themselves to clinical trials. In 2009, Jabre et al. published the largest clinical trial to date involving ketamine 2 mg per kg for RSI in adults, and comparing it to
etomidate 0.3 mg per kg, both with succinylcholine as the neuromuscular blocking (NMB) agent. There were no significant hemodynamic differences between the two groups. The study concluded that ketamine is a safe alternative to etomidate for endotracheal intubation in critically ill patients, and should be considered in those with sepsis.

In the hemodynamically unstable patient, ketamine or etomidate offer the most reliable method of rapidly achieving unconsciousness while limiting further hemodynamic compromise.

**What is the risk of ketamine in the brain-injured patient?** For many years, the use of ketamine was thought to be contraindicated in brain-injured patients because of the risk of increasing intracranial pressure through increased CBF. Subsequent animal models and later clinical data have refuted this earlier hypothesis.

In uninjured brains, CPP = MAP – ICP where CPP is the cerebral perfusion pressure; MAP is the mean arterial pressure; and ICP is the intracranial pressure. Following brain injury, there is a loss of cerebral autoregulation and CBF is largely dependent on cerebral perfusion pressure, which in turn is largely dependent on mean arterial pressure. Consequently, agents such as etomidate and ketamine that maintain MAP will maintain CBF. This is particularly true in patients with polytrauma where traumatic brain injury and shock may coexist. The dangers of hypotension on the injured brain are well known, and any mechanism by which hypotension can be avoided in traumatic brain injury should be encouraged. In ventilated patients with controlled ventilation, ketamine does not increase ICP. In addition to the neuroprotective effects of maintaining CBF through cerebral perfusion pressure, ketamine has also been found to have other neuroprotective properties. A comprehensive review of the available experimental and clinical evidence for the neuroprotective properties of ketamine was recently published. Animal models show that ketamine inhibits the NMDA-receptor activation, reduces neuronal apoptosis, and reduces the systemic inflammatory response to tissue injury. In the last few years, increasing clinical evidence of the safety of ketamine in brain-injured patients has emerged. It is becoming increasingly clear that ketamine is likely not dangerous in brain-injured patients, and instead may confer advantages over other agents. Most clinical data come from neurosurgical units with invasive intracranial pressure using ketamine as a sedative agent.

Very little of these data have been generated using ketamine as an induction agent in the emergency department setting. There are not yet sufficient data to support using ketamine induction for RSI in all brain-injured patients. If the brain-injured patient is also hypotensive, then ketamine is an excellent choice.

**What is the best induction agent for patients with severe bronchospasm?** Most of the data on the use of induction agents in asthma come from the anesthesia literature in elective surgical cases, from animal models, and from experience using ketamine as a sedating agent in intubated asthmatic patients. Although ketamine is widely accepted and recommended as the induction agent of choice for severe asthma, the data on ketamine use for induction in RSI in asthmatic patients in the emergency department are sparse. Etomidate caused a mild increase in airway resistance in a very small study of nonasthmatic intubated patients. Midazolam data are lacking. Ketamine and propofol both cause bronchodilation in asthmatic patients. In the emergency department, severe bronchospasm raises concerns of significantly decreased venous return and cardiovascular collapse, especially following intubation. While propofol may have some bronchodilatory properties, this possible benefit is outweighed in the unstable asthmatic patient by risks of hemodynamic instability, making ketamine the best choice for induction agent in severe bronchospasm. Etomidate also is a good choice as an induction agent in severe bronchospasm because of its excellent hemodynamic stability. Following intubation, either propofol or ketamine are excellent choices for sedation in the patient with severe bronchospasm.
REFERENCES


