*Review Article*

# Rapid-Sequence Intubation: A Review of the Process and Considerations When Choosing Medications

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## Abstract

**Objective:** To summarize published data regarding the steps of rapid-sequence intubation (RSI); review premedications, induction agents, neuromuscular blockers (NMB), and studies supporting use or avoidance; and discuss the benefits and deficits of combinations of induction agents and NMBs used when drug shortages occur. **Data Source:** A search of Medline databases (1966–October 2013) was conducted. **Study Selection and Data Extraction:** Databases were searched using the terms *rapid-sequence intubation, fentanyl, midazolam, atropine, lidocaine, phenylephrine, ketamine, propofol, etomidate thiopental, succinylcholine, vecuronium, atracurium*, and *rocuronium*. Citations from publications were reviewed for additional references. **Data Synthesis:** Data were reviewed to support the use or avoidance of premedications, induction agents, and paralytics and combinations to consider when drug shortages occur. **Conclusions:** RSI is used to secure a definitive airway in often uncooperative, nonfasted, unstable, and/or critically ill patients. Choosing the appropriate premedication, induction drug, and paralytic will maximize the success of tracheal intubation and minimize complications.

## Keywords

rapid-sequence intubation, ketamine, etomidate, propofol, premedications, induction agents, neuromuscular blockers

## Rapid-Sequence Intubation

Rapid-sequence intubation (RSI) is a process for quickly securing an airway in patients who are at risk for aspiration, have an impending loss of airway in situations such as acute burn or trauma, or in patients with severely impaired gas exchange requiring mechanical ventilation. Classic RSI involves applying cricoid pressure via the Sellick maneuver and successive administration of a rapid-acting induction agent and neuromuscular blocking agent.[1] Unlike a standard tracheal intubation, where bag-mask ventilation is performed while the proceduralist awaits optimal intubating conditions, in RSI, no mask ventilation is performed. Once unconsciousness and paralysis has been achieved, the trachea is quickly intubated with an endotracheal tube.

Optimal pharmacokinetic properties for all RSI medications include the following: rapid onset of action, short duration of action, negligible hemodynamic effects, minimal side effect profile, and quickly reversible.[2] Unlike most clinical scenarios, metabolism of the drug through renal or hepatic pathways is not a primary concern because patients will typically be receiving a single dose. However, because shortages of these agents have become increasingly common, determining which alternative agents to consider is very important (discussed below).

RSI is used in situations where a patient requires intubation and is at risk for aspiration. For operative patients, this includes patients who have not fasted in accordance with the American Society of Anesthesia Practice Guidelines for Preoperative Fasting.[3] The majority of patients who require intubation in the emergency department (ED) and intensive care unit (ICU) should be considered to have a full stomach, and most would qualify for a RSI. Traumatic injury inhibits gastric emptying and is associated with gastric acid secretion; so despite an appropriate fasting interval, most clinicians would consider these patients to require RSI.[4] Chronic conditions that place the patient at a higher risk for aspiration include disease states that involve the gastrointestinal system, such as gastrointestinal reflux disease, diabetes, previous

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esophageal surgeries (esophagogastrectomy), ascites, and small-bowel obstruction. RSI should be considered for these patients.[4,5]

## Data Sources and Selection

This article reviews the process of RSI and the pharmacotherapy used in this process. A search of Medline databases (1966–October 2013) was conducted using a combination of the terms *rapid-sequence intubation, fentanyl, midazolam, atropine, lidocaine, phenylephrine, ketamine, propofol, etomidate methohexital, succinylcholine, vecuronium, atracurium*, and *rocuronium*. Randomized clinical trials, observational studies, meta-analyses, and review articles were included. All articles were in the English language. A manual review of the bibliographies of the available literature was performed with relevant information included.

This review will focus on the pharmacotherapy of medications used for RSI.

## Premedications

Premedications are administered to attenuate the anxiety and potentially negative physiological responses that can occur during tracheal intubation.[6] Optimal timing of premedications depends on the abnormal physiological response of concern. Typical premedications include the following: midazolam, fentanyl, atropine, and lidocaine.[7]

### *Midazolam*

Midazolam is a fast-acting benzodiazepine with a short duration of action indicated for anxiolysis[8] (Table 1). It acts through agonism of γ-aminobutyric acid (GABA).[9] Benzodiazepines share many different pharmacological properties; however, their onset of action, duration of action, and lipophilicity differs between agents. Midazolam is the most liphophilic benzodiazepine and thus rapidly crosses the blood-brain barrier. However, it is rapidly and extensively redistributed, resulting in a very short half-life.[10] A typical dose is 1 to 2 mg, with elderly patients receiving smaller doses, and higher doses given in obese patients. Midazolam is hepatically metabolized through oxidation and has an active renal metabolite, 1-hydroxymidazolam. Significant side effects of midazolam are few, especially when used as a sole agent. However, when other medications are used (ie, fentanyl), respiratory depression can occur.[9] Because of midazolam's excellent pharmacokinetic profile and amnestic properties, it is the authors' opinion that midazolam is the most preferred benzodiazepine for use in a RSI.

### *Fentanyl*

Fentanyl is a synthetic, central-acting opioid agonist used to blunt the sympathetic surge with pain receptor stimulation that occurs with intubation. Examples of some patients at risk for further injury from a sympathetic surge would include those who have lost the ability of cerebral autoregulation and those with acute ischemic heart disease and acute aortic aneurysms or dissections.[7] These patients would benefit from narcotics, and fentanyl is the preferred opioid as a result of its high degree of lipophilicity, lack of histamine release, fast onset, and short duration of action[11] (Table 1). A dose of 1 to 3 μg/kg 3 minutes prior to induction is recommended. It is hepatically metabolized by oxidation and does not have an active metabolite. The most common adverse side effect associated with fentanyl is respiratory depression.[12] Administration of fentanyl over 30 to 60 s should minimize respiratory depression.[7] Chest wall rigidity that can make ventilation nearly impossible can occur with fentanyl. However, this is seen primarily following large doses (eg, 100 μg/kg) and should not be a concern with a 1-time dose as a premedication.[10]

### *Atropine*

The process of intubation can stimulate a strong vagal response, especially in pediatric and neonatal patients. Bradycardia is typically not seen in the adult patient population as a result of most adults having underlying conditions that predispose them to a hyperdynamic response to intubation, as discussed above. However, adults who have received medications that alter conduction properties of the sinoatrial or atrialventricular node, such as β-blockers, calcium channel blockers, amiodarone, or digoxin, in addition to fentanyl, which has vagiotonic properties, are at an increased risk of developing bradycardia.[13] Atropine is used to blunt this response by antagonism of muscarinic receptors of the parasympathetic nervous system.[14] The dose for atropine is 0.01 mg/kg in adults.[6] Atropine is hepatically metabolized and has a quick onset of action (Table 1). The most common side effects of atropine are tachycardia, dry mouth, flushing, and urinary retention.[14]

### *Lidocaine*

Historically, lidocaine has been used to blunt the sympathetic response to intubation in patients with suspected elevations in intracranial pressure (ICP); who receive succinylcholine, which can increase ICP (discussed below); and who have asthma and are experiencing bronchospasm. The sympathetic surge associated with intubation potentially can cause further increases in ICP. The mechanism of lidocaine blunting this response is not completely understood but is thought to work by a combination of suppression of reflexes, inducing peripheral GABA receptor anesthesia, depression of the brain stem, slowed cerebral metabolism, and stabilization of membranes by decreasing the rate of depolarization and repolarization.[15] Many have refuted this claim and have suggested that the practice does

**Table 1.** Properties of Premedications, Induction Agents, and Neuromuscular Blockers.

| Agent | Dose | Onset of Action | Elimination Half-life | Avoid | Consider |
|---|---|---|---|---|---|
| Midazolam | Premedication: 1-2 mg IV[8]; induction: 0.1-0.3 mg/kg IV or IM[7] | 60-90 s[8] | 1-4 hours[8] | • Premedication: patients who have significant opioid medications on board<br>• Induction: hemodynamically unstable, heart failure, elderly, liver disease | • Premedication: anxious patients, predicted difficult intubation<br>• Induction: No IV access |
| Fentanyl | 1-3 µg/kg IV[8] | <30 s[2] | 2-4 hours | • Patients who will not tolerate a decrease in their minute ventilation<br>• Hypotension<br>• Muscle rigidity | • Patients where blunting of the sympathetic response is critical |
| Atropine | 0.02 mg/kg IV in adults[6] | 2-16 minutes[8] | 2-3 hours[8] | • Tachycardic patients | • Adults with bradycardia<br>• Patients with copious secretions |
| Lidocaine | 1.5 mg/kg IV[6] | 45-90 s[7] | 7-30 minutes[7] | • Not needed in most patients with adequate induction and paralysis | |
| Phenylephrine | 50-200 µg IV[67] | <30 s[66] | 5 minutes[68] | | |
| Methohexital | 1.5 mg/kg IV[2] | Less than 30 s[48] | 5-10 minutes[48] | • Septic shock<br>• Hypotension | • Head injuries<br>• Elevated ICP<br>• Hemodynamically stable patients |
| Propofol | 1-2 mg/kg IV[2] | 15-45 s[52] | 5-10 minutes[2] | • Hypotension<br>• Low ejection fraction | • Hemodynamically stable patients<br>• Bronchospasm<br>• Head Injuries<br>• Elevated ICP |
| Etomidate | 0.3 mg/kg IV[5] | 15-45 s[6] | 3-12 minutes[6] | • Septic shock<br>• Seizure disorder | • Hemodynamic instability |
| Ketamine | 1-2 mg/kg IV[2]; 4-10 mg/kg IM[2] | 30 s[8] | 5-15 minutes[2] | • Hypertensive patients<br>• Significant oral secretions | • Hemodynamic instability<br>• Asthma |
| Succinylcholine | 1.5 mg/kg IV; 3-4 mg/kg IM (maximum 150 mg)[76] | 1-1.5 minutes[76] | 3-6 minutes[76] | • Malignant hyperthermia<br>• Hyperkalemia<br>• Patients at risk for hyperkalemia | • Patients without contraindications |
| Rocuronium | 0.6-1.2 mg/kg IV[76] | 1-2 minutes[76] | 30-67 minutes[76] | • Inability to mask ventilate | • Contraindications to Succinylcholine |
| Vecuronium | 0.1-0.2 mg/kg IV[77] | 2-4 minutes[77] | 20-60 minutes[77] | • Potential prolonged intubation<br>• If succinylcholine and rocuronium available | • If succinylcholine and rocuronium shortage |

Abbreviations: IV, intravenous; IM, intramuscular; ICP, intracranial pressure.

more harm than good.[15] A decrease in mean arterial pressure by 30 mm Hg following lidocaine administration was reported in a study of patients receiving lidocaine prior to RSI.[16] Additionally, 3 studies have shown that ICP still

increases when patients receive lidocaine, it is just a more modest increase (Table 2).[17-19] Despite its reported lack of efficacy, lidocaine is still widely used. The typical dose of lidocaine is 1.5 mg/kg (common 100 mg), and it has a relatively quick onset of action (Table 1).[6] It is recommended to administer lidocaine 3 minutes prior to RSI to blunt the increase in ICP. However, this could result in an unacceptable delay when emergent intubation is indicated. Lidocaine undergoes hepatic metabolism.[20] Other side effects associated with lidocaine include hypotension, which can further decrease cerebral perfusion pressure in a patient with a head injury and arrhythmia. However, none of the aforementioned studies assessed for adverse effects.[21] Additionally, lidocaine interacts with several medications, including dronedarone (proarrhythmic), amiodarone (increases risk of hypotension), and monoamine oxidase inhibitors (causes hypotension).[7]

## Induction Agents

Rapid administration of the induction agent quickly followed by neuromuscular blockade helps achieve optimal conditions for intubation.[11] The selection of the induction and paralytic agents is based not only on patient-specific factors but also on the specific drug characteristics. Induction agents that are commonly used for RSI include the following: barbiturates, propofol, etomidate, ketamine, and midazolam. Studies evaluating the use and side effects of induction agents and neuromuscular blockers (NMBs) are summarized in Table 2.[22-47]

### *Barbiturates*

Traditionally, barbiturates were commonly used for induction purposes, but with the introduction of propofol and barbiturate drug shortages, use has fallen dramatically.[48-50] A commonly used barbiturate has been thiopental; however, it is no longer available for use in the United States. The alternative short-acting barbiturate is methohexital, and its dosage is 1.5 mg/kg.[2] Barbiturates work by way of agonism of GABA receptors. At low doses, they increase GABA activity through decreasing GABA dissociation from the receptor. At high doses, barbiturates directly stimulate the GABA receptor. Barbiturates undergo hepatic metabolism. Methohexital does not have any active metabolites.[51]

The most common side effects associated with methohexital include respiratory depression, venodilation, and myocardial depression. Methohexital should be avoided in patients with hypotension when other agents such as ketamine or etomidate are available.[51] Methohexital also decreases cerebral metabolic oxygen demand, which decreases ICP and cerebral blood flow. However, caution should be used in using this agent in patients with traumatic brain injuries given its ability to cause hypotension. Methohexital can also cause histamine release, which may exacerbate reactive airway disease. Some excitatory symptoms such as hiccups and twitching have also been noted with methohexital use. Distal thrombosis and tissue necrolysis can occur if methohexital is given intra-arterially or because of extravasation as a result of its alkaline pH.[51]

A small, retrospective study comparing methohexital with etomidate in patients that were undergoing intubation found no significant difference in the rate of successful intubations or hemodynamic effects (Table 2).[22] Another small study, The SHRED Study, randomized patients to thiopental, fentanyl, or midazolam as an induction agent during RSI. Fentanyl was found to be the most hemodynamically neutral of the 3 agents.[23]

### *Propofol*

Propofol is a highly lipid-soluble, phenolic derivative, which is a GABA agonist and is used as an induction agent for RSI.[52] The dosage of propofol used for induction in healthy patients is 1.5 mg/kg IV (common, 100-200 mg).[6] Because obese patients have an increased volume of distribution but a decreased rate of elimination as compared with lean patients, actual body weight should be used for dosing of propofol.[53]

Propofol's pharmacodynamic profile is well suited to RSI[53] (Table 1). Its high degree of lipophilicity allows it to cross the blood-brain barrier very rapidly, thus resulting in a quick onset of action. Propofol very quickly redistributes into peripheral tissues and is rapidly metabolically cleared, thus, resulting in a short duration of action. The rate of elimination and central volume of distribution is decreased in elderly patients and, therefore, lower doses of propofol should be considered (50-100 mg).[52]

Because of its hepatic metabolism to water-soluble sulfate and glucuronide conjugates, it is suitable in patients with hepatic or renal impairment.[52] Propofol decreases ICP, so it is an appropriate agent to use for induction in patients with increased ICP. A study of 6 patients with head injuries who received a bolus of propofol for induction showed a mean decrease in ICP of 14 mm Hg[24] (Table 2). In patients with bronchospasm, propofol is an appropriate induction agent because of its mild bronchodilating effects. It has no analgesic properties[53] and is the drug of choice for induction in pregnant women because it is a category B drug.[2]

A disadvantage of propofol is that it has calcium channel and a β-adrenergic receptor antagonist properties, which may induce hypotension and bradycardia. Caution should be exercised in patients with volume depletion, hypotension, or a reduced ejection fraction.[1] Concurrent use of opioids, abdominal surgery, weak physical state, female gender, and advanced age have all been associated with an exaggerated hypotensive response.[53] With prolonged (>72 hours) and high-concentration (>75 μg/kg/min) infusion, there is a risk

**Table 2.** Premedication, Induction Agent, and Neuromuscular Blocker Studies.

| References | Population | Design | Control Group | Treatment Group | Primary Outcome | Key Secondary Outcomes |
|---|---|---|---|---|---|---|
| Samaha et al (1996)[17] | 22 patients undergoing neurosurgery and intubation | Randomized, double-blind study | Esmolol 1.5 mg/kg before intubation | Lidocaine 1.5 mg/kg before intubation | Significant decrease in CPP in esmolol and lidocaine groups ($P < .05$) | ICP and CPP increased significantly in both groups following intubation ($P < .05$) |
| Bedford et al (1980)[18] | 20 patients with brain tumors undergoing intubation | Randomized, double-blind study | Placebo | Lidocaine 1.5 mg/kg before intubation | Increase in ICP was less in the lidocaine group ($P = .03$) | |
| Hamill et al (1981)[19] | 22 patients with brain tumors undergoing intubation | Prospective, randomized study | Laryngotracheal lidocaine (4 mL of 4%) | Lidocaine 1.5 mg/kg IV | No increase in ICP occurred after intubation in the IV lidocaine group, but there was an increase in the laryngotracheal lidocaine group ($P < .05$) | |
| Diaz-Guzman et al (2010)[22] | 46 patients who underwent endotracheal intubation | Retrospective, observational, single-center, cohort study | Etomidate | Methohexital | Rate of successful intubation after 1 attempt was 78% in the methohexital group and 83% in the etomidate group | Change in hemodynamics did not differ between groups |
| Sivilotti et al (1998)[23] | 86 patients undergoing RSI in the emergency department | Prospective, randomized, double-blind study | | Thiopental, midazolam, fentanyl | Fentanyl was the most hemodynamically neutral agent | Mortality was unaffected by treatment assignment |
| Herregods et al (1988)[24] | 6 adult patients with severe head injuries | Case series | | Propofol | Mean decrease in ICP at 25 minutes to 11 mm Hg ($P < .05$) | |
| Hildreth et al (2009)[25] | 30 adult trauma patients requiring rapid-sequence induction | Prospective, randomized, controlled study | Midazolam/Fentanyl | Etomidate | Mean cortisol level was lower in the etomidate group compared with the midazolam/fentanyl group ($P < .05$) | Longer ICU length of stay ($P < .05$), more ventilator days ($P < .01$), longer hospital length of stay ($P < .01$) in the etomidate group |
| Mohammed et al (2006)[26] | 152 adult patients with septic shock | Retrospective, single-center study | Placebo | Etomidate | Incidence of relative adrenal insufficiency in the etomidate group was higher than in the placebo group ($P = .0077$) | |
| Watt and Ledingham (1984)[27] | 428 trauma patients admitted to the ICU | Retrospective, single-center study | Morphine/Etomidate | Morphine with or without benzodiazepine | 25% reduction in mortality when changed from morphine/etomidate to morphine with or without benzodiazepine in ventilated patients ($P < .005$) | |
| Absalom et al (1999)[28] | 35 critically ill patients who needed an anesthetic | Prospective, randomized, single-center study | Thiopentone | Etomidate | No patient in the thiopentone or etomidate groups had evidence of absolute adrenal failure; post-CST cortisol levels tended to be higher in the thiopentone group as compared with the etomidate group ($P = .052$) | |
| Vinclair et al (2008)[29] | 40 critically ill patients without sepsis in a university hospital | Prospective, observational cohort study | | Etomidate | 12 hours after etomidate administration, 80% of patients developed adrenal insufficiency; 48 hours after etomidate administration, 9% of patients developed adrenal insufficiency; 72 hours after etomidate administration, 7% of patients developed adrenal insufficiency | |
| Albert et al (2011)[30] | 2854 patients in 14 studies | Meta-analysis | Non-etomidate | Etomidate | Etomidate versus non-etomidate anesthesia showed an increased risk ratio for adrenal insufficiency of 1.64 (range 1.52-1.77); etomidate versus non-etomidate anesthesia showed an increased risk ratio for mortality of 1.19 (1.10-1.30) | Mortality within the subset of sepsis was maintained, with a risk ratio of 1.22 (1.11-1.35), but not for trials without sepsis, with a risk ratio of 1.15 (0.97-1.35) |

*(continued)*

**Table 2. (continued)**

| References | Population | Design | Control Group | Treatment Group | Primary Outcome | Key Secondary Outcomes |
|---|---|---|---|---|---|---|
| Schenarts et al (2001)[31] | 31 patients in the ED requiring intubation | Prospective, randomized study | Midazolam | Etomidate | 4 Hours post-CST, 100% of patients in the midazolam group as compared with 30% of patients in the etomidate group had normal CST results; 12 and 24 hours after CST, results did not differ between groups ($P = 1.0$) | |
| Cotton et al (2008)[32] | 137 trauma patients who underwent CST | Retrospective, single-center study | No etomidate exposure | Etomidate | Etomidate exposure was higher in the nonresponder group ($P < .01$) | |
| Cuthbertson et al (2009)[33] | 499 patients with septic shock | An a priori multicenter, randomized, double-blind, placebo-controlled trial | No etomidate exposure | Etomidate | Proportion of nonresponders to CST was higher in patients who received etomidate in the 72 hours before trial than in other patients (61.0% vs 44.6%, $P = .004$); etomidate associated with a higher 28-day mortality in univariate analysis ($P = .02$) and after correction for severity of illness (42.7% vs 30.5%; $P = .06$ and $P = .03$) in 2 multivariate analyses | Hydrocortisone did not alter the mortality of patients receiving etomidate (45% vs 40%) |
| Kolenda et al (1996)[34] | 35 patients with severe head injuries | Prospective, randomized study | Fentanyl and midazolam | Ketamine and midazolam | Lower vasopressor requirement in the fentanyl group as compared with the ketamine group ($P < .05$ on day 1) | Average 8 mm Hg higher CPP and a 2 mm Hg higher ICP in the fentanyl group |
| Albanese et al (1997)[35] | 8 patients with traumatic brain injury | Case series | Not applicable | Ketamine | Decrease in ICP at all 3 doses administered ($P < .05$) | No significant change in CPP following ketamine administration |
| Bourgoin et al (2003)[36] | 25 patients with severe head injury | Prospective, randomized, double-blind study | Sufentanil-midazolam | Ketamine-midazolam | No significant differences in ICP and CPP between groups | |
| Langsjo et al (2003)[37] | 9 healthy male volunteers | Case series | Not applicable | Ketamine | MAP was slightly elevated following ketamine administration ($P < .0001$) | Ketamine increased CBF in a concentration-dependent manner |
| Bourgoin et al (2005)[38] | 30 patients with severe traumatic brain injury | Prospective, randomized study | Sufenanil-midazolam | Ketamine-midazolam | 2-Fold increases in drug concentrations did not significantly increase ICP or CPP in either group | |
| Jabre et al (2009)[39] | 655 patients needing sedation for intubation | Randomized, controlled, single-blind trial | Etomidate | Ketamine | Intubation conditions did not differ significantly between the etomidate and ketamine groups (median intubation difficulty score 1 [IQR = 0-3] in both groups; $P = .70$) | Adrenal insufficiency was significantly higher in the etomidate group compared to the ketamine group (OR = 6.7, CI = 3.5-12.7) |
| Smischney et al (2012)[40] | 84 patients undergoing general anesthesia | Randomized, double-blind, placebo-controlled study | Propofol | Ketofol | Propofol was more likely to cause a 20% reduction in systolic blood pressure (48.8% vs 12%, $P < .001$) | |
| Sagarin et al (2003)[41] | 1023 patients undergoing RSI | Query of a prospectively collected database of ED intubations | Not applicable | Midazolam | The mean dose of midazolam for induction in adults was 0.05 mg/kg | |
| Biane et al (2012)[42] | 131 critically ill patients intubated with succinylcholine | Prospective, observational study | Not applicable | Succinylcholine | Length of ICU stay prior to intubation influenced K ($P < .001$) | |
| Perry et al (2008)[43] | Randomized controlled or controlled clinical trials comparing rocuronium and succinylcholine | Meta-Analysis | Succinylcholine | Rocuronium | Succinylcholine was superior to rocuronium (RR = 0.86) | |

*(continued)*

**Table 2. (continued)**

| References | Population | Design | Control Group | Treatment Group | Primary Outcome | Key Secondary Outcomes |
|---|---|---|---|---|---|---|
| Marsch et al (2011)[44] | 401 critically ill patients requiring emergent RSI | Prospective, randomized, controlled, single-blind, single-center study | Succinylcholine | Rocuronium | No difference in oxygen desaturations between succinylcholine and rocuronium ($P = .67$) | |
| Davison and Holland (1989)[45] | Patients requiring rapid-sequence induction for emergency surgical operations | Prospective, randomized, single-center study | Succinylcholine | Atracurium, vecuronium | Mean time to 80%-90% neuromuscular blockade was shorter with succinylcholine as compared with vecuronium and atracurium ($P < .01$) | |
| Magorian et al (1993)[46] | 50 patients requiring rapid-sequence induction for anesthesia | Prospective, randomized, single-center study | Succinylcholine, vecuronium | Rocuronium | Onset time of rocuronium 0.9 mg/kg and 1.2 mg/kg rocuronium and succinylcholine (1 mg/kg) were similar; onset times for rocuronium 0.6 mg/kg and vecuronium (0.1 mg/kg) were much longer | |
| Smith et al (2002)[47] | 100 patients requiring emergency rapid-sequence oral intubation | Prospective, blinded study | Vecuronium | Rocuronium | Intubation was successful in 95% of patients in the vecuronium group and 100% in the rocuronium group; the percentage of patients having good or excellent jaw relaxation and vocal cord exposure was similar between groups (vecuronium 79%, rocuronium 77%) and pressure (48.8% vs 12%, $P < .001$) | |

Abbreviations: MAP, mean arterial pressure; CPP, cerebral perfusion pressure; ICP, intracranial pressure; IV, intravenous; RSI, rapid-sequence intubation; ICU, intensive care unit; CST, cosyntropin stimulation test; ED, emergency department; K, potassium.

of propofol infusion syndrome.[53,54] However, this should not be a concern when used solely as an induction agent. Pain on peripheral administration of propofol is common, which can be attenuated by the use of lidocaine, use of a larger peripheral vein, or central venous administration.[52]

Traditionally, it has been thought that propofol is contraindicated in patients with an egg allergy. However, the 5 major allergens associated with an egg allergy are isolated from the egg white. Propofol is an oil-water emulsion that uses soybean oil and egg lecithin. Egg lecithin is a highly purified phosphatidyl from egg yolk, so theoretically, propofol should not induce an allergic response in patients with an egg allergy. The isopropyl or phenyl groups and not the lipid vehicle have been deemed responsible for the few, reported IgE-mediated anaphylactic reactions associated with propofol.[55]

## Etomidate

Etomidate is an imidazole-derived sedative hypnotic that is a commonly used induction agent for RSI. Etomidate stimulates GABA receptors to block neuroexcitation and induce unconsciousness. The dosage range is 0.2 to 0.6 mg/kg (common, 20-50 mg), with the most common dose used being 0.3 mg/kg. In hemodynamically unstable patients, consideration of dose reduction to 0.2 mg/kg can be considered. An adjusted body weight is recommended in morbidly obese patients.[2] The main advantages of etomidate are that it has minimal cardiovascular effects, decreases ICP, and does not cause histamine release.[25] Etomidate also has a quick onset of action, short duration of action, and undergoes hepatic elimination[56] (Table 1). Etomidate has no analgesic effects. Following etomidate administration, myoclonus, which can be mistaken for seizure activity, can occur with an incidence rate of 22% to 63%.[57] It is clinically inconsequential and is extinguished when the NMB takes effect. Pain on injection is a common side effect[57] and is secondary to the diluent propylene glycol. Etomidate has also been associated with increased postoperative nausea and vomiting when compared with thiopental.[2] Etomidate causes a moderate reduction in intraocular pressure (IOP). Additionally, etomidate causes a 20% to 30% decrease in cerebral blood flow, resulting in a moderate lowering of ICP that can last several minutes.[57]

Because etomidate inhibits 4 cytochrome P450 enzymes involved in corticoneogenesis and 11β-hydroxylation of glucocorticoid and mineralocorticoid precursors, it may induce prolonged suppression of cortisol and aldosterone.[26,58] Recently, several small studies have shown that a single dose of etomidate is associated with adrenal insufficiency in critically ill,[26,28-30] ED,[31] and trauma[25,32] patients (Table 1). However, most of these studies were small and underpowered to assess mortality. There has been a discordance of information regarding etomidate-associated mortality, with 1 small study demonstrating no difference in mortality[32] and a recent meta-analysis showing an association between etomidate and mortality in septic shock patients. However, the meta-analysis contained many low- to moderate-quality studies, and the clinical illness scores of the etomidate and non-etomidate groups were not matched a priori.[30] Some experts recommended giving replacement steroids to those who receive etomidate in an effort to counteract the adrenal suppressive effects.[33] An a priori subgroup analysis of the Corticus Study demonstrated that etomidate administration was an independent predictor of mortality (Table 1) not offset by steroid administration. This is only a subgroup analysis and was not powered to evaluate these outcomes prospectively. At this time, there is not enough evidence to recommend use or avoidance of etomidate for RSI in patients with the concern for adrenal insufficiency. Further studies need to be conducted to further clarify etomidate's association with mortality.[33]

## Ketamine

Ketamine has some of the ideal characteristics of an RSI induction agent. Ketamine is highly lipophilic and readily crosses the blood-brain barrier and causes both functional and electrophysiological brain dissociation. Intense amnesia occurs secondary to ketamine's dissociative effects, inducing a trancelike cataleptic state[37] by noncompetitive inhibition of glutamine at the *N*-methyl-D-aspartic acid (NMDA) receptors in the thalamocortical and limbic central nervous system (CNS). In addition to its amnestic effects, and unlike any other induction agent, ketamine provides analgesia.[1] It does this through antagonism of the NMDA receptor, which potentiates opiate receptor activity.[59] The induction dose of ketamine is 1 to 2 mg/kg (common, 100 mg). Ketamine is hepatically metabolized to an inactive metabolite, norketamine, which is renally excreted (Table 1).[59] A prospective, randomized, double-blind study was conducted that compared ketamine with etomidate and showed no difference in intubating conditions (Table 2).[39]

Ketamine exerts sympathomimetic effects such as increase in heart rate, blood pressure, and cardiac output by stimulating CNS outflow and lessening the reuptake of catecholamines. Because of these sympathomimetic effects, ketamine is an excellent induction agent for patients with hypotension.[60] However, ketamine can worsen hypotension and exacerbate myocardial depression in patients who are catecholamine depleted. This would include patients who have had prolonged hypotension; a maximum dose of 1.5 mg/kg is recommended in these patients.[2] Historically, it was thought that ketamine should be avoided in patients with increased ICP, secondary to early studies demonstrating increased cerebral oxygen consumption, increased cerebral blood flow, and increased ICP.[61,62] Several, more-recent studies have demonstrated that in sedated and mechanically ventilated patients,

ketamine does not increase ICP (Table 2).[34-39] Also, when ketamine is used for sedation and analgesia in patients with head injuries, mean arterial pressure is maintained, vasopressor requirements are decreased, and cerebral perfusion pressure is maintained as compared with patients who received a combination of benzodiazepines and opioids.[37-39] Given data supporting mortality in association with hypotension in patients with blunt head injuries, ketamine appears to be an excellent choice for an induction agent in this patient population.[36] Ketamine's sympathetic stimulation normally overrides its direct negative cardiac inotropic effect. However, in patients with severe heart failure, the negative inotropic effects may predominate. This may result in cardiac output–related hemodynamic instability, making ketamine a less favorable induction agent in patients with severe heart failure.[63]

Ketamine relieves bronchospasm by dilating the bronchial smooth muscle and stimulating the pulmonary β-receptors; so it is an appropriate agent for asthmatics. Ketamine can significantly increase oral secretions during its duration of activity, which can decrease the ability to visualize glottic structures during laryngoscopy. However, this is rarely a clinical issue within the first minute after administration, in the time frame associated with RSI.[63]

Ketamine is a phencyclidine analog and can be associated with emergence delirium, nightmares, and hallucinations.[60] Traditional thinking was that a benzodiazepine, such as midazolam, should be administered prior to the ketamine to prevent the emergence reactions and hallucinations.[1,64] However, recent studies have reported that prophylactic administration of a benzodiazepine does not decrease emergence reactions but does increase the incidence of respiratory depression and can prolong recovery.[65,66]

A combination of ketamine and profofol, "ketofol," has been suggested as a possible induction regimen, with each drug thought to partially combat the unwanted side effects of the other agent. A study in 84 patients undergoing general anesthesia randomized patients to ketofol or propofol. Improved hemodynamic stability was demonstrated in the ketofol group following induction[40] (Table 2). However, additional studies need to be conducted in critically ill patients.

### *Midazolam*

Midazolam's use as a premedication has been discussed above; however, it can be used as an induction agent as well. Its use as an induction agent is more commonly seen in the pediatric population. The induction dose of midazolam is 0.2 to 0.3 mg/kg[11] (Table 1). When used alone, it has a slow onset of action (up to 5 minutes) and causes incomplete loss of consciousness[2,11] (Table 1). If opioids are administered concurrently, the onset of action improves to 90 s.[2] Both times are unacceptable in the setting of a RSI.[2] Patients receiving midazolam as an induction agent can experience a dose-related decrease in systemic vascular resistance and myocardial depressive effects, and a dosage reduction should be considered in patients who are volume depleted or hemodynamically unstable. Following the large dose required for induction of midazolam, elderly patients and those with heart failure or liver disease would be expected to experience a prolonged sedative effect with midazolam.[2]

### *Phenylephrine*

Vasodilation and myocardial depression can occur from induction agents used in RSI. This hypotension may be intensified in critically ill patients for a variety of reasons, including underlying acid-base abnormalities, sepsis, hemorrhage, and shock.[13] Phenylephrine can be administered to patients who experience hypotension from other premedications such as lidocaine, midazolam, or fentanyl or induction agents such as propofol or ketamine. The common dose of phenylephrine is 50 to 200 μg in adult patients, repeated as necessary to treat hypotension. Phenylephrine is hepatically metabolized and has a quick onset of action and elimination half-life (Table 1). The most common adverse effect associated with phenylephrine is reflex bradycardia.[67]

## Neuromuscular Blocking Agents

Emergent intubations in areas outside of the operative environment are associated with complications such as hypoxemia, airway-related complications, and cardiovascular instability greater than 20% of the time.[68] NMBs have been reported to be associated with decreased complications associated with emergent airway management and improved intubating conditions.[69-72] Yet the use of NMBs outside of the operative environment for an emergent intubation remains controversial because of the potential inability to intubate or mask ventilate.[68] Caution should be exercised in the use of a NMB if this potential exists (high body mass index, a history of a previous difficult intubation, or nonreassuring airway exam findings). If a NMB blocker is to be used, an agent that has a rapid onset and quick metabolism should be considered. The 2 NMBs that are most often used in RSI are succinylcholine and rocuronium.[10]

There are 2 types of NMBs: (1) depolarizing and (2) nondepolarizing. Depolarizing NMBs resemble acetylcholine (Ach) structurally. The NMB binds to and activates the Ach receptors on the motor endplate, resulting in depolarization of the postjunctional neuromuscular membrane, yielding continuous stimulation of the motor endplate. Nondepolarizing NMBs competitively block Ach receptors at the postjunctional cholinergic nicotinic receptors, but they do not activate the Ach receptors.[73] Paralysis ends when the NMB dissociates from the Ach receptors. Muscle contraction will not reoccur until the neuromuscular

junction returns to the resting state (repolarizes) and then is depolarized again.[1] Duration of effect differences between the options depends both on the affinity to the receptor and the half-life of the NMB at the site of activity.

## Succinylcholine

Succinylcholine is the only depolarizing NMB currently available in the United States. Succinylcholine's rapid onset and short duration of action make it an ideal agent for use in RSI (Table 1). The dosage of succinylcholine is 1 to 2 mg/kg total body weight (common, 100 mg). In rare situations where intravenous access is not able to be obtained, succinylcholine may be administered intramuscularly at a dose of 3 to 4 mg/kg (common, 300 mg); however, the onset of action will be delayed to 3 to 4 minutes. Repeated doses (6 mg/kg) of succinylcholine should be avoided because of the potential development of a phase 2 block.[74] Phase 1 blockade is what is typical of depolarizing NMBs and is preceded by muscle fasciculation. It is the result of succinylcholine stimulating the Ach receptors on the motor nerve, causing repetitive firing. A phase 2 blockade is when administration of depolarizing agents results in characteristics associated with competitive blockade and is thought to occur secondary to an increase in cellular sodium and potassium permeability.[75] With repeated dosing of succinylcholine, there may be a potentiation of succinylcholine's vagal effects, leading to bradycardia and hypotension. Bradycardia occurs most often in infants and children and can be prevented with pretreatment using atropine.[76]

An important consideration with succinylcholine use is its stability at room temperature; it has a shelf life of 14 days. For prolonged storage, it is recommended that it be refrigerated at a temperature of 36°F to 48°F.[77]

Denervating neuromuscular diseases, such as myasthenia gravis, cause a functional decrease in the number of Ach receptors at the neuromuscular junctions secondary to antibody-mediated autoimmune destruction of these receptors. A dose increase to greater than 2 mg/kg is required for these patients.[1]

Upregulation in the number of Ach receptors secondary to the decrease in the amount of Ach being released from motor nerve terminals occurs in the setting of Lambert-Eaton myasthenic syndrome. Given the competitive antagonist action of these agents, patients with Lambert-Eaton myasthenic syndrome would have increased effects to nondepolarizing NMBs, and avoidance of nondepolarizing NMBs is recommended. Response to succinylcholine appears to be normal, and a dose reduction is not needed.[78]

Pseudocholinesterase is a circulating enzyme that metabolizes succinylcholine, and patients with a deficiency of this enzyme can remain paralyzed for up to 6 to 8 hours after a single dose of succinylcholine. Thus, succinylcholine should be avoided in patients with known pseudocholinesterase deficiency. A relative decrease in this enzyme can occur in patients with liver disease, renal disease, anemia, pregnancy, chronic cocaine use, amphetamine abuse, increased age, connective tissue disease, and certain malignancies. The clinical significance of this deficiency is minimal, and no dosage adjustments need to be made.[6]

The most serious side effects of succinylcholine administration include malignant hyperthermia and hyperkalemia. Calcium is the central regulator of contraction and metabolism in the muscle. The sarcoplasmic reticulum tubules contain calcium ions, which when released lead to the activation of actin and myosin, resulting in muscle contraction. Normally, muscle relaxation occurs when the ATPase pumps return calcium back to the sarcoplasmic reticulum. During malignant hyperthermia, triggering agents, such as succinylcholine, cause an abnormally high rate of release of calcium through calcium release channels. The ryanodine receptor is the calcium release channel that mediates calcium release within the skeletal muscle cell. Mutation in the ryanodine gene on chromosome 19 that codes this receptor accounts for 50% of the patients who are susceptible to malignant hyperthermia.[79]

Malignant hyperthermia should be considered in patients who have recently received a triggering agent such as succinylcholine and exhibit signs of hypermetabolism. Clinical signs include fever, a rapid rise in end-tidal $CO_2$, tachycardia, and muscle rigidity. Muscle rigidity can affect the masseter muscle and can make intubation difficult or impossible. Rhabdomyolysis of skeletal muscle can occur with subsequent increases in calcium, potassium, and creatine kinase concentrations.[80] For patients with malignant hyperthermia, an arterial blood gas analysis will demonstrate mixed respiratory and metabolic acidosis.

When malignant hyperthermia is suspected, the triggering agent should be discontinued, and treatment should start immediately. Dantrolene is the treatment used and binds directly to the ryanodine receptor to inhibit calcium release from the sarcoplasmic reticulum and reduces intracellular calcium concentrations. Dantrolene is dosed at 2.5 mg/kg. Each vial of dantrolene has to be reconstituted with 60 mL of sterile water and is difficult to dissolve. This can be a labor-intensive therapy for pharmacy to prepare. For the other physiological derangements associated with malignant hyperthermia, supportive care should be given.[79]

Hyperkalemia following succinylcholine administration typically causes a 0.5 to 1 mEq/L rise in serum potassium.[1,77] Patients with acute hyperkalemia secondary to diabetic ketoacidosis or acute renal failure do not have a contraindication to succinylcholine. An increase of 0 to 0.5 mEq/L would be expected in these patients. A meta-analysis evaluated patients with and without renal failure and no patient was found to have an increase in potassium greater than 0.5 mEq/L.[80] If the patient has symptomatic hyperkalemia, an alternative agent such as rocuronium should be considered.[2]

In certain patient populations, the rise in potassium can be significantly higher.[1,77] These groups include patients with the proliferation of extrajunctional cholinergic receptors, including those with prolonged immobilization, crush injuries, burns, myopathies such as muscular dystrophy, denervating diseases or injuries such as multiple sclerosis, amyotrophic lateral sclerosis, stroke, and spinal cord injury.[77] For acute denervating nerve injuries, the upregulation of Ach receptors will not occur for 5 to 15 days after the insult. Serum potassium may rise as much as 5 to 15 mEq/L, putting these patients at risk for arrhythmias and cardiac arrest.[81] Because of the delay in the upregulation of the Ach receptors, it is generally safe to give succinylcholine within the first 24 hours following a nerve injury or stroke.[78] In patients with burns, the percentage of the body surface area affected does not correlate well with the degree of the hyperkalemia. Patients with burns comprising 8% of the total body surface area have developed severe hyperkalemia.[2] Receptor sensitivity generally lasts 2 to 6 months postinjury, but many clinicians consider any patient with persistent denervation always at risk for hyperkalemia.[77] One study evaluated for risk factors associated with hyperkalemia in patients intubated with succinylcholine showed length of stay influenced potassium[42] (Table 2).

Other side effects of succinylcholine include increased ICP and increased IOP. The effect of succinylcholine on ICP is controversial, with some studies showing a minor increase of 5 to 10 mm Hg, whereas other studies showed no effect.[1] Succinylcholine has been shown to increase IOP by 5 to 10 mm Hg for 2 to 6 minutes.[82] There have been no reported cases of vitreous extrusion after succinycholine administration in a patient with an open globe injury. Therefore, anesthesiologists still use succinylchline in patients with open globe injuries with or without a defasciculating agent.[83]

## *Nondepolarizing NMBs*

With its rapid onset and short duration, succinylcholine is an ideal NMB for a RSI, and there is currently no nondepolarizing NMB that has pharmacodynamic and pharmacokinetic properties similar to succinylcholine. The closest match and most commonly used drug is rocuronium[74] (Table 1).

*Rocuronium.* Rocuronium is a nondepolarizing NMB that inhibits depolarization by antagonism of Ach receptors. The dosage of rocuronium is 0.6 to 1.2 mg/kg. Pharmacokinetics and adverse effect profiles must be considered when determining which agent to use for paralysis during RSI. Because of rocuronium's longer duration of action as compared with that of succinylcholine, caution should be used in patients who may be difficult to bag-mask ventilate[76] (Table 1). One study[43] (Table 2) demonstrated succinylcholine's superiority, whereas another[44] showed no difference in oxygen saturation between groups.

*Vecuronium.* Vecuronium is another nondepolarizing NMB that inhibits depolarization by antagonism of Ach receptors.[75] The dose of vecuronium used for RSI is 0.08 to 0.1 mg/kg. However, given vecuronium's longer onset of action and duration of therapy, it is generally not recommended for paralysis during RSI (Table 1). Yet with the increasing frequency of drug shortages (discussed below), including succinylcholine and rocuronium, the utilization of vecuronium may be necessary. Studies[45,46] (Table 2) demonstrate that succinylcholine has a much faster onset of action compared with vecuronium. One final study[47] in Table 2 comparing rocuronium and vecuronium shows successful intubations in both groups.

Historically, depolarizing NMBs such as vecuronium or rocuronium at one-tenth of their normal dose were administered prior to succinylcholine. This practice was thought to decrease fasciculations associated with succinylcholine, which were postulated to increase ICP. However, this practice is no longer recommended[7] because the lack of evidence.[84]

*Sugammadex.* Sugammadex is an altered γ-cyclodextrin that is used for immediate reversal of neuromuscular blockade. At a dose of 16 mg/kg, sugammadex forms a firm bond with rocuronium and terminates the neuromuscular blockade within 3 minutes by reducing rocuronium's plasma concentration at the neuromuscular junction.[85] Rocuronium's strong binding properties to sugammadex have been demonstrated through X-ray crystallography.[86] The plasma activity of rocuronium is decreased to zero because Sugammadex binds rocuronium 1:1. Sugammadex has specific binding properties for the aminosteroidal nondepolarizing muscle relaxants and has the strongest binding affinity with rocuronium, followed by vecuronium, and finally by pancuronium. Sugammadex has 2.5 times the affinity and selectivity for rocuronium as compared with vecuronium. Sugammadex has no binding affinity for succinylcholine, cisatracurium, atracurium, or mivacurium. The FDA has not approved sugammadex because of concern over hypersensitivity or allergic reactions, so it is currently not available in the United States.[87,88]

*Neostigmine.* Neostigmine is an acetylcholinesterase inhibitor used to reverse nondepolarizing muscular blocking agents such as vecuronium. It stops the hydrolysis of Ach by competing with Ach for attachment to acetylcholinesterase at sites of cholinergic transmission. The dosage most commonly used is 0.03 to 0.07 mg/kg, and its onset of action is within several minutes. When administered, significant bradycardia can occur, and an anticholinergic agent such as glycopyrrolate should be given before or concurrently with neostigmine to prevent bradycardia.[89]

**Table 3.** Advantages and Disadvantages of Different Combinations of Induction Agents and Paralytics to Be Considered During a Drug Shortage.

| | Succinylcholine | Rocuronium | Vecuronium |
|---|---|---|---|
| Methohexital | Methohexital and succinylcholine both increase ICP. Methohexital and succinylcholine both can be given IM | Methohexital has a much shorter duration of action than rocuronium. This combination could be problematic in a patient who is difficult to intubate. Both agents have a longer duration of action in liver dysfunction. | Methohexital has a much shorter duration of action than vecuronium. This combination could be problematic in a patient who is difficult to intubate. Both agents have a longer duration of action in liver dysfunction |
| Propofol | Both propofol and succinylcholine can cause bradycardia | Propofol has a much shorter duration of action than rocuronium. This combination could be problematic in a patient who is difficult to intubate. Both agents have a longer duration of action in liver dysfunction | Propofol has a much shorter duration of action than vecuronium. This combination could be problematic in a patient who is difficult to intubate. Both agents have a longer duration of action in liver dysfunction |
| Etomidate | Etomidate and succinylcholine are both very rapid acting and have short durations of action | Etomidate has a much shorter duration of action than rocuronium. This combination could be problematic in a patient who is difficult to intubate. Both agents have a longer duration of action in liver dysfunction | Etomidate has a much shorter duration of action than vecuronium. This combination could be problematic in a patient who is difficult to intubate. Both agents have a longer duration of action in liver dysfunction |
| Ketamine | Ketamine and succinylcholine both are negative inotropes. Both ketamine and succinylcholine can be given IM | Ketamine has a much shorter duration of action than rocuronium. This combination could be problematic in a patient who is difficult to intubate. Both agents have a longer duration of action in liver dysfunction | Ketamine has a much shorter duration of action than rocuronium. This combination could be problematic in a patient who is difficult to intubate. Both agents have a longer duration of action in liver dysfunction |
| Midazolam | Midazolam will need 60 to 90 s to work prior to succinylcholine administration | Midazolam has a much shorter duration of action than rocuronium. This combination could be problematic in a patient who is difficult to intubate. Both agents have a longer duration of action in liver dysfunction | Midazolam has a much shorter duration of action than vecuronium. This combination could be problematic in a patient who is difficult to intubate. Both agents have a longer duration of action in liver dysfunction |

Abbreviations: IM, intramuscular; ICP, intracranial pressure.

## Drug Shortages

Drug shortages are a growing problem that limits the ability to pick the most optimal drug regimen for utilization during RSI. In the past year, nearly all the drugs mentioned in this review have been in limited supply in some regions.[90] Properties of alternate combinations of induction agents or NMBs should be considered when the optimal choice is not currently available (Table 3). When doing so, the pharmacodynamic properties must be considered to avoid inappropriate consequences. For example, giving an induction agent (propofol) in the absence of the premedication (midazolam) with a significantly shorter duration of action than the paralytic (vecuronium) can increase the risk of patient awareness. Another consideration is the additive side effect profile that could exacerbate a baseline condition. An example of this would be the worsening of a bradycardia by the use of propofol and succinylcholine. One final question to consider is the off-label use of drugs that would not be a standard rapid-sequence medication. Although many drugs can provide conditions that are suitable for standard intubation, the onset of action and metabolism of the drugs may not fit the criteria of a RSI. For example, dexmedetomidine is an α-2-adrenergic agonist used for sedation in the ICU. Following the administration of the intravenous load, in theory, it could provide sedating conditions that would be enough for tracheal intubation to take place. Because of the delayed onset of action (minutes for the infusion to be completed and pharmacological effects to take place), the intubation would be a standard intubation and not a RSI. The authors would recommend caution in the off-label use of medications for RSI.

## Summary

RSI is used to secure a definitive airway in often uncooperative, nonfasted, unstable, and critically ill patients. Choosing the appropriate premedication, induction drug, and paralytic will maximize the success of tracheal intubation and minimize complications.

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