RAPID SEQUENCE INTUBATION GUIDELINES

I. Rapid sequence intubation (RSI) is a technique for achieving intubation using a series of discrete steps, including administration of pharmacologic agents , which maximize likelihood of success and minimize complications.

II. RSI is a procedure for patients with critical disease or traumatic process. The selection of technique and specific agents is determined individually for each patient and each situation. Different techniques, equipment and agents may be used for children and complex or rescue situations.

III. RSI results in rapid unconsciousness (induction) and neuromuscular blockade (paralysis) and is the preferred method of endotracheal intubation for patients who have not fasted and are at greater risk for vomiting and aspiration. The goal of RSI is to intubate the trachea without the use of Bag-Valve-Mask ventilation, which is often necessary when using sedatives alone (titrated to effect).

IV. Proper technique minimizes aspiration risk by avoiding the need for positive pressure ventilation (BVM)

V. RSI involves administration of weight-based doses of an induction agents (such as etomidate) immediately followed by a paralytic agent (such as succinylcholine or rocuronium) to ideally render the patient rapidly unconscious and paralyzed (within 1 minute), increasing chances of success.

VI. Harmful reflexes associated with laryngoscopy and intubation without induction and paralysis are avoided; (increased Intracranial pressure, intraocular pressure, blood pressure, heart rate and bronchospasm).

VII. When to implement; Whenever not in "crash" intubation situation such as cardiac arrest and when a "difficult" intubation is not anticipated. All other situations consider RSI.

VIII. When not to implement: *RSI is not indicated in a patient who is unconscious and apneic.* This is considered the "crash" airway and immediate BVM ventilation and endotracheal intubation without pre-treatment, induction or paralysis is indicated

INDICATIONS FOR INTUBATION

I. **Airway obstruction**

II. **Inability to maintain patent airway/tone**
   a. Swelling of upper airway as in anaphylaxis or infection
   b. Facial/neck trauma with oropharyngeal bleeding/hematoma
   c. Inability to protect airway against aspiration
   d. Severe cognitive impairment (GCS<8) leading to aspiration of vomit, secretions, blood, teeth or foreign bodies

III. **Ventilatory compromise**
   a. Hypoventilation
   b. End result of failure to maintain and protect airway
   c. Large pneumothorax, hemothorax, flail chest or pulmonary contusion
   d. Prolonged respiratory efforts leading to profound fatigue/failure such as status asthmaticus or severe COPD

IV. **Failure to adequately oxygenate**
   a. Severe hypoxemia despite supplemental oxygen
   b. End result of failure to maintain and protect airway or failure to ventilate
   c. Large pneumothorax, hemothorax, flail chest or pulmonary contusion
   d. Diffuse pulmonary edema
   e. Acute Respiratory Distress Syndrome
   f. Large pneumonia or air-space disease
   g. Pulmonary embolism
   h. Cyanide toxicity, carbon monoxide toxicity, methemaglobinemia

V. **Anticipation of deteriorating course** that will eventually lead to maintain airway patency or protection
   a. Severe hemorrhagic shock
   b. Combative trauma patient with life-threatening injuries needing procedures (chest tubes, etc)
   c. Stab wound to neck with expanding hematoma
   d. Intracranial hemorrhage with altered mental status, need for blood pressure control, maximize oxygenation & ventilation, airway protection
   e. Cervical spine fractures with concern for edema, loss of airway reflexes/patency
   f. Septic shock with high minute-ventilation and poor peripheral perfusion

CONTRAINDICATIONS

I. **Absolute**
   a. Total upper airway obstruction; requires surgical airway
   b. Total loss of oropharyngeal/facial landmarks; requires surgical airway

II. **Relative**
   a. Anticipated "difficult" airway, in which endotracheal intubation may be unsuccessful, resulting in reliance on successful BVM ventilation
   b. "Crash" airway is indicated for patient in cardiac arrest; immediate BVM ventilation, intubation or both should be performed without medications

"The Ritual of the Seven "Ps of RSI"

1. PREPARATION
2. PRE-OXYGENTATION
3. PRE-TREATMENT
4. PARALYSIS with Induction
5. POSITIONING
6. PROVE PLACEMENT
7. POST-INTUBATION MANAGEMENT

PREPARATION

I. Assemble equipment/ensure all is operational
   a. Various sizes of endotracheal tubes/stylets/syringes/test balloon prior to insertion
   b. Laryngoscope handle/blades (various types & sizes)/check that light is operational
   c. IV lines: two with patency checked
   d. Suction ready at bedside
   e. Cardiac monitor
   f. Pulse oximetry
   g. BVM, 100% oxygen
   h. Medications: specific drug/dosage formula, draw up/label
   i. End-tidal CO2 detector, capnography if available
   j. Method to secure endotracheal tube
   k. "Rescue ", "difficult" airway kit/adjuncts available in room
      i. King Airway, Combitube, LMA, and surgical cricothyrotomy equipment
      ii. Gum elastic bougie

II. Assemble staff
   a. EMS staff as appropriate and available
   b. Trauma Team, Code/Critical Care Team
      i. Respiratory Therapist, if available
      ii. CRNA or Anesthesiologist if available

III. Assess airway upon patient arrival
   a. The mnemonic LEMONS on the last page can help predict a difficult intubation

PRE-OXYGENATION

I. Apply Non-Rebreather mask at 15 liters per minute as soon as possible
The patient should breathe the high flow oxygen for 5 minutes prior to attempting intubation
   a. This establishes super-saturated oxygen reservoir in lungs by replacing nitrogen (nitrogen "washout"), allowing patient to maintain saturation during paralysis and intubation. Gives up to eight minutes of apnea before desaturation (<90%) occurs (less time in children, patients with higher metabolic demand for oxygen and the critically ill)

II. Alternative technique if time is short; have patient take 8 deep vital capacity breaths with hi-flow oxygen

PRE-TREATMENT

Pretreatment phase of RSI involves the delivery of medications to modify the physiologic response during and after intubation. The mnemonic LOAD is used to remember the pretreatment drugs.

I. **L** *Lidocaine 1*-1.5 mg/kg IV
   - The use of *lidocaine* in RSI has been advocated to blunt the intracranial pressure rise associated with RSI but the evidence supporting its effectiveness is not clear.

II. **O** Opiates *fentanyl* (*sublimaze*) 2-9 mcg/kg IV
   - Opiates can be used to attenuate the sympathetic responses to intubation
   - Pretreatment with *fentanyl* (2 mcg/kg), immediately prior to the induction of anesthesia, significantly reduces the hemodynamic response to endotracheal intubation

III. **A** Atropine Anticholinergic agent
   - Use in children to prevent bradycardia/asystole (seen with *succinylcholine*)
   - Consider in adults who are to be redosed with *succinylcholine* to prevent possible bradycardia

- *Atropine* (pediatrics): 0.02 mg/kg IV (min 0.1 mg);adult: 0.5-1 mg IV

IV. **D** Defasciculating agents (choose one)
- Defasciculation refers to decreasing/eliminating the muscle fasciculations (twitches) that occur in response to the initial depolarizing effect of *succinylcholine*. These muscle contractions can produce a rise in intracranial and intraocular pressure.
- Use defasciculating doses of paralytic agents in patients with head injury or open-globe eye injuries
- Can use 1/10th the intubating dose of any available paralytic agent
  - *Succinylcholine* 0.15 mg/kg IV
  - *Rocuronium* 0.1 mg/kg IV

V. If possible, allow three minutes for medications to distribute.

VI. *The disadvantage of pre-medications includes the addition of time and complexity to the procedure and may be eliminated depending on the clinical situation.*

PARALYSIS (with Induction)

This step involves the administration of an induction agent followed rapidly by a paralytic agent, giving the procedure the name "rapid sequence".

I. Do not ventilate until patient is intubated or reoxygenation is required as indicated by oxygen saturation falling below 90%.

II. **INDUCTION AGENTS** provide a rapid loss of consciousness that facilitates ease of intubation.
- **Etomidate** (Amidate) 0.3mg/kg IV-rapid onset, short duration, cerebroprotective, not associated with hypotension, hemodynamically neutral in comparison with other agents. Most common induction agent used in United States
- **Ketamine** (Ketalar) 1-2 mg/kg/IV- "dissociative" state, analgesic properties, bronchodilator, may increase intracranial pressure. Consider for patients with asthma or anaphylactic shock. Avoid in patients with known/suspected aortic dissection, abdominal aortic aneurysm and acute MI.
- **Propofol** (Diprivan) 2mg/kg/IV- rapid onset, short duration, cerebroprotective. Caution: propofol is myocardial depressant and decreases systemic vascular resistance
- Midazolam (Versed) *Not recommended as induction agent due to delayed time to induction, some propensity for hypotension at induction doses (20mg for 70Kg patient) and prolonged duration of action*

III. **PARALYSIS AGENTS** are administered immediately after induction agent.

Does NOT provide sedation, analgesia, or amnesia so potent induction agent is essential
- Depolarizing neuromuscular blocker;
  Succinylcholine (Anectine) 1- 1.5 mg/kg IV- rapid onset (45-60sec), shortest duration of action (8-10 minutes). Use with caution in patients with known/suspected hyperkalemia, burns, crush injuries, intra-abdominal sepsis and those with neuromuscular disease.
- Nondepolarizing neuromuscular blocker;
  Rocuronium (Zemuron) 1-1.2mg/kg IV- slightly longer onset of action (60-75 sec) and longer duration of action (30-60 minutes). Does not result in muscle depolarization or defasciculation and does not exacerbate hyperkalemia. Use with caution in patient for whom "difficult" intubation is possible
  Vecuronium (Norcuron) 0.1-0.2 mg/kg IV – less desirable sue to longer onset of action (2-3 min) and longer duration (30-60min) Does not result in muscle depolarization or defasciculation and does not exacerbate hyperkalemia

POSITIONING

I. Ensure patient position is ideal to improve visualization.

II. In cases where cervical spine injury is suspected, intubation must be performed without movement of the head, best provided by an experienced assistant.

III. Place patient in sniffing position to help align the axes & facilitate visualization of the glottic opening

IV. Sellick Maneuver may be initiated to prevent gastric contents regurgitating into the lungs, but recent studies may show that cricoid pressure does not significantly decrease the risk of aspiration or enhance visualization of the glottis opening.

V. Firm **B**ackward, **U**pward and **R**ightward **P**ressure (BURP) on patient's thyroid cartilage may improve view

VI. A patient who is hypoxemic during intubation attempts should undergo BVM ventilation with 100% oxygen to raise PO2 levels.

VII. Issues of Intubation

a) Failure to adequately sweep the tongue out of the way. By inserting the blade as far to the right as possible the intubator can more effectively force the tongue to the left side of the mouth and out of the way.

b) Failure to place the tip of the laryngoscope deep enough into the mouth. Pressure placed too far forward on the tongue (instead of the curved blade in the vallecula or the straight blade past it) will not allow adequate lifting of the epiglottis and obstruct the view of the cords.

PROVE PLACEMENT

I. Visualize the ET tube passing through the vocal cords

II. Confirm tube placement (essential)
   a. Observe color change on colormetric end-tidal CO2 detector
   b. If available, utilize wave-form capnography
   c. Use 5-point auscultation method; listen over each lateral lung field, the left axilla & left supraclavicular region for presence of good breath sounds. There should be no sounds of air movement over the stomach

POST-INTUBATION MANAGEMENT

I. Secure ET tube, note depth of initial tube placement on documentation

II. Initiate mechanical ventilation

III. Obtain a CXR
   a. Assess pulmonary status (remember CXR does not confirm placement, but assesses the tube height above the carina). Ensure that mainstem intubation has not ocurred

IV. Administer sedative/analgesia for patient comfort, decreased oxygen demand and to decrease ICP, especially if patient is paralyzed with longer-acting paralytic agent (vecuronium)

V. Obtain arterial blood gases, if facility is capable

VI. Document all components of the procedure accurately/ completely including time, tube size, depth of insertion and number of attempts

VII. Maintain rigorous patient monitoring and oversight for continued ventilatory effectiveness, depth of sedation and paralysis, hemodynamic stability and patient comfort

COMPLICATIONS

Esophageal intubation
Right mainstem intubation
Failure to intubate
Hypotension
Aspiration
Iatrogenic induction of obstructive airway
Pneumothorax
Dental/oral trauma
Post intubation pneumonia
Vocal cord avulsion

LEMONS Assessment for Difficult Intubation

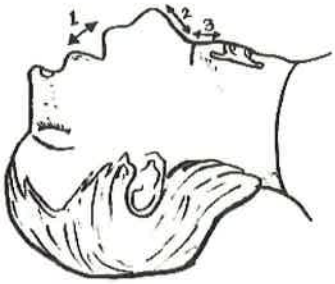
Assess the probability of success during tracheal intubation in advance. A critically ill patient may not be able to cooperate with all sections of LEMON assessment.

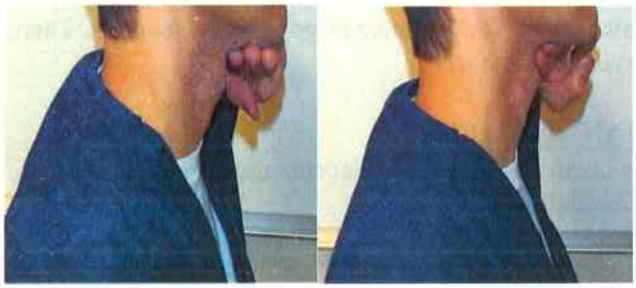
L: Look externally; physical features such as small mandible, large tongue and a short, bull neck are all anatomic "red flags" for difficulty

E: Evaluate the 3-3-2 Rule

Chance for success is increased if the patient;

- Can insert 3 of his/her own fingers longitudinally between teeth (1)
- Can accommodate 3 finger-breadths between hyoid bone & mentum (2)
- Is able to fit 2 finger-breadths between hyoid bone & thyroid cartilage (3)

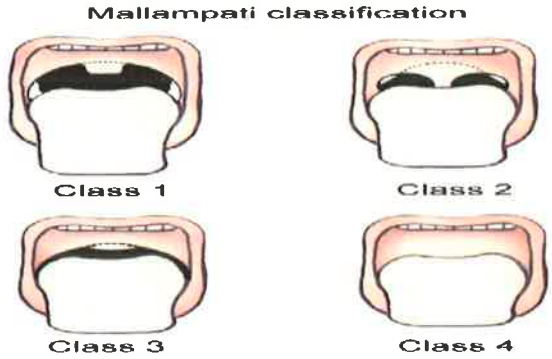




Hyo-mental distance (2) Thyro-hyoid distance (3)

M: Mallampati Classification

Mallampati assessment is best accomplished when patient is seated, with open mouth & phonating.
A cursory assessment of the patient in supine position can be made to gain perspective on the size of the mouth opening and the likelihood that the tongue and oropharynx may be factors in successful intubation. Class 1 and 2 should have no difficulty, Class 3 moderate difficulty, & Class 4 may have major difficulty.



O: Obstruction

Three signs of upper airway obstruction are;

Difficulty swallowing secretions
Stridor (upper airway inspiratory sound due to tracheal swelling)
Muffled (hot potato) voice

N: Neck Mobility

Inability to move the neck affects optimal visualization of the glottis. Cervical spine immobilization in trauma and such arthritic conditions such as rheumatoid arthritis and ankylosing spondylitis can affect neck mobility

S: Saturation

An oxygen saturation < 85% portends an impending desaturation that can occur very rapidly. This does not allow much time to perform the intubation.

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Medications used in Tracheal Intubation

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Medications for Rapid Sequence Endotracheal Intubation

In order to achieve a successful intubation, various classes of medications are needed to achieve specific pharmacologic effects. These effects include providing sedation, analgesia from pain, amnestic effects, anesthesia, anticholinergic effects to control secretions, and paralysis.

Intubation, when performed using the rapid sequence intubation (RSI) protocol, is typically discussed in several stages (ie, pretreatment, induction and paralysis, and post-intubation); each stage requires specific medications. The medication choices described below provide the specific effects that are essential to creating the optimal conditions for endotracheal intubation. For complete information, see Rapid Sequence Intubation.

The image below depicts an inserted endotracheal tube.

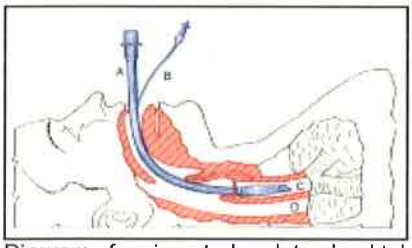

Diagram of an inserted endotracheal tube. Image courtesy of Wikimedia Commons.

Stage 1 - Pretreatment

Preoxygenation

Oxygenation before rapid sequence intubation (RSI) is a critical step aimed at maximizing blood oxygen saturation levels and creating an oxygen reservoir in the lungs to eliminate the need for bag-valve-mask (BVM) ventilation. Preoxygenation may be the most critical of all steps involved in RSI. The oxygen reservoir permits continued oxygenation of pulmonary circulation, eliminating the need for BVM ventilation for the period of apnea after induction and paralysis to minimize the risk of stomach insufflation and aspiration. This process is dependant on a properly fitted mask with a constant and unbroken seal maintained with 2 hands.

Nitrogen constitutes about 80% of ambient air. During oxygenation, oxygen replaces nitrogen at the alveolar level. This results in what is known as *nitrogen washout*, thus creating an oxygen reservoir in the functional residual capacity of the lungs. Ninety-five percent of nitrogen elimination occurs in 2 minutes. Preoxygenation before induction and paralysis allows up to 8 minutes of apnea time in healthy adults before arterial oxygen desaturation below 90% occurs. The desaturation rate is more rapid in children because of their higher baseline metabolic rate. The same is true for adults who are obese or acutely ill, given their higher oxygen demand.

Also, expect rapid desaturation in patients with primary respiratory problems, such as congestive heart failure (CHF), acute respiratory distress syndrome (ARDS), and diffuse pneumonia. These patients all share a physiologic shunt, which may require some form of positive end-expiratory pressure (PEEP) to ensure maximal alveolar distention and recruitment. In addition, if positive-pressure ventilation is required at any time to increase the oxygen saturation above 90%, keep ventilations to a minimum of 10 slow (2 seconds per breath) breaths per minute. This rate/depth provides ample ventilation while avoiding overcoming the lower esophageal sphincter opening pressure of 20-25 cm of water.[1]

Preoxygenation may be accomplished through various protocols, depending on the characteristics of the patient. The most straightforward protocol is to deliver high-flow oxygen via a nonrebreather face mask to a spontaneously breathing patient for 3 minutes. Baraka and colleagues also showed that 8 deep breaths over 60 seconds, by using full vital capacity, gives the same partial oxygen tension (PaO_2) as the standard 3 minutes of tidal volume breathing of 100% BVM oxygenation.[2] The time required to reach oxygen desaturation is the same for either technique. The deep breath method should be considered a reasonable alternative to the traditional 3-minute tidal volume technique when time is of the essence.

Although the goal is to avoid BVM ventilation after induction and paralysis, continued bagging may be necessary for patients whose blood oxygen saturation drops below 90% for any reason (eg, unsuccessful intubation, patient characteristics noted above). If necessary, bagging should be performed with cricoid pressure in order to compress the esophagus and minimize stomach insufflation and aspiration.

Physiologic Responses to Direct Laryngoscopy and Premedication

Pressor response

The direct stimulation of the pharynx, larynx, and trachea by the laryngoscope blade itself can cause a pressor response, which is a sympathetic nervous system reflex with a measurable increase in plasma catecholamines consisting of transient increase of blood pressure (up to a 35-mm Hg increase in the mean arterial pressure [MAP]) and a heart rate increase (up to 30 bpm). These hemodynamic changes typically last less than 5 minutes. In rare cases, transient dysrhythmias may be induced. Despite this, no study to date has linked the pressor response to subsequent clinical deterioration, although it is still considered useful to minimize its effect.

Numerous agents have been used for attenuation of the pressor response, including lidocaine, fentanyl, sufentanil, alfentanil, and esmolol.

Lidocaine, a class IB antidysrhythmic agent with local anesthetic properties, is the most common agent for this purpose and has shown mixed results in its ability to attenuate the response. In 1961, Bromage showed that its intravenous use blunted the cardiovascular response of intubation.[3] Whether this has any clinical significance is unclear. In a 1994 report, Lev and Rosen examined 25 studies pertaining to lidocaine in intubation. Of those studies, 60% claimed that lidocaine produced some benefit in attenuating the cardiovascular response to intubation.[4]

The literature does support the use of lidocaine as a cough suppressant, probably achieved by means of either brainstem depression or peripheral anesthesia of the trachea and the pharyngeal cough receptors. Studies of the effects of lidocaine on the cardiovascular response to intubation are less convincing. The data are confusing, conflicting, and, for the most part, not adequately controlled.

Fentanyl, a rapid-acting synthetic opioid, is also effective in blunting the sympathetic response to laryngoscopy and intubation. Opioids may be superior to lidocaine in blunting the pressor response at appropriate doses. Opioid receptors are found in the cardiovascular regulatory center, the sympathetic nervous system, the vagal nuclei, and the adrenal medulla. These precise locations of receptors enable fentanyl to significantly blunt the hemodynamic responses to hypopharyngeal noxious stimulation.

Pharmacokinetically, fentanyl has a rapid onset of 1 minute and a duration of action of 30 minutes. The dose for complete sympathoadrenal blockade is greater than 7 mcg/kg, although recommended doses for pretreatment for intubation in the emergency department is 3 mcg/kg to avoid hypotension in patients dependent on sympathetic tone. Although thoracic and abdominal muscular rigidity is a concern, the incidence is extremely low and usually only observed when high doses (ie, >15 mcg/kg) are used.

Sufentanil and **alfentanil** possess a more rapid onset and shorter duration of action than fentanyl, making these agents potentially more attractive as pharmacologic adjuncts against the hemodynamic responses of intubation. Alfentanil has the fastest onset of action of all the opioids. In 1990, Pathak and colleagues reported that alfentanil 15-30 mcg/kg effectively blocks both the MAP and heart-rate responses to laryngoscopy and intubation without complications.[5]

Esmolol is essentially the only beta-blocker that could be used as a pretreatment agent because it is beta-1 selective, it possesses a rapid onset of action, and it has an ultrashort duration of effect. Its onset of action is within seconds, and its elimination half-life is 9 minutes. Its dose in this situation is 1 mg/kg administered as a simple bolus 2 minutes before intubation.

Feng and colleagues compared lidocaine 2 mg/kg, fentanyl 3 mcg/kg, and esmolol 2 mg/kg and found that only esmolol offered reliable protection against increases in both heart rate and systemic blood pressure.[6] Helfman and colleagues conducted a similar study in 1991 and found that fixed doses of lidocaine 200 mg, fentanyl 200 mcg, and esmolol 150 mg produce similar results because only the esmolol provided consistent and reliable protection against the pressor response.[7] Other studies have showed that when 2 pretreatment drugs are used together, a technique known as synergism occurs, which is a beneficial result with a marked decrease in the dosing of each of the involved drugs. However, certain patients may benefit from esmolol during RSI, including patients with acute coronary syndrome and those with suspected dissecting thoracic aneurysms.

Again, though avoiding any potential transient increase in heart rate and blood pressure in critical patients is prudent, no study has established a direct relationship between this autonomic reflex and an increase in mortality risk.

Intracranial hypertension

Just as physical stimulation of the airway causes a sympathomimetic reflex response, the same manipulation causes a transient increase in intracranial pressure (ICP). Possible mechanisms of action include simply coughing and gagging and subsequent transmission of intrathoracic pressure to the cranium. Also, the catecholamine release induced by airway manipulation and its inherent increased MAP probably plays a role. Remember, cerebral oxygenation is determined by cerebral perfusion pressure (CPP), which is defined as CPP = MAP - ICP. Normal CPP is 80-100 mm Hg and must be maintained above 50 mm Hg to maintain cerebral autoregulatory functions. These cerebral autoregulatory mechanisms are impaired in patients with significant head injuries, subarachnoid hemorrhage, or acute elevations in hemodynamics in association with head injury.

Normal ICP is less than 10 mm Hg, but it may rise above 60 mm Hg in patients with cerebral injuries. Even in patients without head injury, endotracheal suction and laryngeal manipulation cause an average increase of 22 mm Hg. Any significant increase in ICP or decrease in MAP may result in a critical decrease in CPP, contributing to a further cycle of cerebral ischemia/edema and elevation of ICP with a possibility of permanent neurologic dysfunction as a sequela. Again, although the exact meaning and significance of these data (mostly derived in the operating room) are unclear, regulating this response in the at-risk patient seems prudent.

Lidocaine 2 mg/kg blunts the cough and gag reflex, thereby halting transmission of intrathoracic pressure to the cerebrum. However, in a patient who is paralyzed, this is not a concern. The decrease in ICP is most probably related to its sympatholytic activity. Lidocaine also decreases cerebral metabolism and stabilizes cell membranes by blocking membrane sodium channels. Prophylactic lidocaine also obtunds the rise in intraorbital pressure that accompanies tracheal manipulation. This response is independent of paralytic agents.

Donnegan and colleagues have shown reductions in ICP elevation resulting from the administration of lidocaine versus placebo.[8] Again, they postulated that its effect was due to its dual ability to not only attenuate a rise in MAP but also directly decrease the cough and gag reflex.[8]

However, studies do not consistently demonstrate the effectiveness of lidocaine for these indications. Furthermore, no study has shown lidocaine to lower ICP and decrease morbidity in patients with intracranial pathology undergoing RSI in the emergency department.[9]

The best results have been demonstrated in patients who are paralyzed, suggesting that paralysis itself may be the best method to attenuate any potential elevations of ICP by inhibiting the cough reflex. In a patient who is paralyzed, the effectiveness of lidocaine is not clear, but it may be beneficial in blunting the pressor response and, indirectly, ICP elevations.

Some have also advocated in the past the use of "defasciculating doses" of a paralytic agent in order to prevent the defasciculations encountered with the administration of succinylcholine, which have been thought to possibly increase ICP. These doses were typically one-tenth the paralyzing dose of a noncompetitive paralytic agent, such as vecuronium or pancuronium. This practice has fallen out of favor in the setting of suspected elevated ICP because of the lack of supporting data.

Children and infants tend to have a more pronounced vagal response to laryngoscopy, which can result in bradycardia. For this reason, the current recommendation for children younger than 1 year undergoing direct laryngoscopy is administration of atropine 0.02 mg/kg, independent of succinylcholine use. Previous recommendations indicated that all children younger than 10 years receive atropine prior to intubation, but this has now fallen out of favor because of the lack of supporting data.

Pretreatment Medications

Pretreatment medications are administered 2-3 min before intubation.[10, 11, 12]

Table 1. Pretreatment Medications (Open Table in a new window)

Drug Name Generic (Trade)	Adult Dose	Onset of Action	Duration of Action	Advantages	Cautions
Fentanyl	1-2 mcg/kg slow IV push (over 1-2 min)	Immediate	0.5-1 h	Primary pretreatment drug to provide sedation and analgesia; decreases hypertensive response to intubation though at this time, no conclusive evidence supports the use of opioids in routine RSI[13]	Hypotension; chest wall rigidity at high doses (ie, >15 mcg/kg)
Lidocaine (Xylocaine)	1.5 mg/kg IV push	1-2 min	10-20 min	Useful in patients with asthma/COPD to decrease hypertensive response	Hypotension
Atropine	0.02 mg/kg (usually about 0.4 mg) IV push Typically administered for pediatric patients ≤1 y	2-4 min	Up to 4 h	Antisialagogue	Tachycardia
Vecuronium (Norcuron)	Defasciculating dose: 0.01 mg/kg IV push (typically about 1 mg, or 10% of intubation dose)	...	...	Decreases fasciculation and potassium release from cells; particularly useful if intend to use succinylcholine	Avoid higher doses that may produce paralytic effect
Rocuronium (Zemuron)	Defasciculating dose: 0.06 mg/kg IV push (typically about 10% of intubation dose)	...	...	Decreases fasciculation and potassium release from cells; particularly useful if intend to use succinylcholine	Avoid higher doses that may produce paralytic effect

Stage 2 - Induction

The induction phase of rapid sequence intubation (RSI) is used to produce anesthesia and rapid unresponsiveness. In 1934, John Lundy introduced the first case in which thiopental was used. Today, numerous pharmacologic classes of drugs are used, although etomidate is the most common agent used in the ED for this purpose.

The ideal drug produces rapid unconsciousness, has a short duration of action, and causes minimal alterations in hemodynamics, respirations, and intracranial pressure (ICP). It should also have the ability to be easily stored and readily available for use. Although most sedatives cause some cardiovascular depression, these effects are exaggerated in patients who are acutely ill, many of whom are hypovolemic or hypotensive. The clinical status of a given patient often dictates which induction agent should be used. Factors to consider include altered hemodynamics, suspected ICP abnormalities, and reactive airway disease.

Etomidate

Etomidate is now considered the criterion standard of induction agents in its use in RSI. Etomidate is an ultrashort-acting nonbarbiturate hypnotic agent that has been used since the 1970s in Europe. Its advantages are rapidity of

onset, short duration of action, lack of cardiodepressant effects, marked safety in patients with head injury, and minimal adverse effects. Indeed, these features support it as the ideal sedative for RSI.

The dose for RSI is 0.3 mg/kg IV, or a typical adult dose of 20 mg. Etomidate is available as a solution of 20 mg/mL and may be stored at room temperature with a long shelf life. Although it does not have any direct effect on muscle tone, it may enhance the effects of paralytics.

Etomidate is a potent sedative hypnotic induction agent via its binding $GABA_2$ receptor, though it lacks analgesic properties. It is a carboxylated imidazole that is both water- and lipid-soluble. It rapidly accumulates in vascular organs, producing unconsciousness within 30 seconds and reaching peak brain concentration in 1 minute. Its high potency causes unconsciousness within 1 arm-brain circulation time and lasts less than 10 minutes after a simple bolus injection. Because of its lipophilic properties, the redistribution half-life is 2.6 minutes, which accounts for its short duration of action. It is rapidly hydrolyzed in the liver and plasma, forming an inactive metabolite excreted in the urine.

Unlike other induction agents, etomidate does not depress the cardiovascular system because the sympathetic outflow and baroreceptor reflexes are maintained. However, because it lacks analgesic effect, laryngoscopy itself may induce sympathetic stimulation, and slight transient hypertension may ensue.

Etomidate acts on the CNS to stimulate gamma-aminobutyric acid (GABA) receptors and, in doing so, depresses the reticular activating system. The electroencephalogram (EEG) changes are similar to those produced by barbiturates as the patient passes rapidly through light to deep levels of surgical anesthesia. This agent decreases cerebral oxygen consumption by 45% and cerebral blood flow by 34%, thereby decreasing ICP. Interestingly, only a minimal change in the cerebral perfusion pressure (CPP) is noted. This unique property of acutely decreasing the ICP while maintaining normal hemodynamics places etomidate in a class alone in the arena of induction agents. These properties and its extreme and rapid potency make etomidate the drug of choice for virtually all cases of RSI.

Etomidate blocks 11B-hydroxylase, the enzyme that converts 11-deoxycortisol to cortisol in the last step in this corticosteroids synthesis. This transient dose-dependent inhibition of adrenocortical activity may last 5-15 hours; however, in the setting as an induction agent, this appears to be clinically insignificant.

Hohl et al conducted a systematic review to compare a bolus dose of etomidate with other induction agents for rapid sequence intubation.[14] Measured outcomes included adrenal function, mortality, and health services utilization. Pooled data suggest that etomidate has no significant effect on mortality and that it suppresses adrenal function transiently. Evidence to show a difference in ventilator use or in ICU or hospital lengths of stay was insufficient.

More recently, Chan et al performed a meta-analysis to assess the effects of a single bolus dose of etomidate in RSI and determine its effect on adrenal insufficiency and mortality in septic patients. Though they reported a higher risk of mortality and adrenal insufficiency in the etomidate group, these 2 endpoints were not related. Further, conclusions were drawn from pooled, methodologically flawed trials. At this time, no appropriately powered, properly randomized, controlled trial of single-dosed etomidate shows harm, and because of such, it remains one of the safest options for RSI.[15, 16]

Nausea, vomiting, myoclonus, and laryngospasm are other reported adverse effects but are usually attenuated by paralysis and are more of a concern when etomidate is used in conscious sedation. No absolute contraindications to its use in RSI exist.

Ketamine

Ketamine is a phencyclidine (PCP) derivative that been available for more than 30 years. It is an ideal induction agent for RSI because it produces rapid sedation, has a brief duration of action, and is extremely potent. It possesses both analgesic and amnesic properties and is stable at room temperature. This agent also has a long shelf life.

Ketamine is highly lipid soluble and accumulates rapidly in highly vascular organs when it undergoes rapid redistribution. Because of this feature, anesthesia is produced in less than 1 minute. The half-life of redistribution is only 7-11 minutes, and the half-life of elimination is 2-3 hours after its degradation in the liver.

Most other anesthetic agents work by depressing the reticular activating system. However, ketamine acts by interrupting pathways between the thalamocortical and limbic systems. Patients enter a trancelike state and are unaware of surroundings, even with their eyes wide open. Because of the properties of ketamine, it is often described as a dissociative anesthetic. The patient has slow nystagmus in a nonsleep (sort of cataleptic) state associated with a dose-related CNS depression characterized by profound amnesia and analgesia. The dose for induction is 2 mg/kg IV with clinical recovery in 10-15 minutes.

Ketamine is the induction agent of choice in patients with bronchospasm because it is the only agent with bronchodilatory properties. Although the bronchial smooth muscle relaxes, airway reflexes remain intact. Bronchial secretions are also increased, which may decrease the incidence of mucus plugging in patients with asthma. Studies have shown that when ketamine is used in patients with asthma who are dependent on ventilators, respiratory acidosis and airway pressures are decreased compared to control subjects.

The direct negative inotropic effect on the myocardium is masked by an increase in blood pressure, heart rate, cardiac output, and an overall decrease in myocardial oxygen consumption. Ketamine is not recommended in patients with uncontrolled hypertension or in those in whom hypertension should be avoided (eg, elevated ICP, aortic dissection or aneurysm, myocardial infarction). On the other hand, ketamine may be ideal for those with hypotension, such as those experiencing hemorrhagic, hypovolemic, or septic shock. The only real clinical concern for the use of ketamine in RSI is its inherent property as a potent cerebral vasodilator.

Past reports stated that it may increase ICP; however, more recent studies indicate that this may have been overstated. Kropf et al found similar hemodynamic properties compared with etomidate.[17] In fact, newer research suggests that ketamine may improve cerebral perfusion pressure and may in fact have neuroprotective properties.[18, 19]

The tendency to produce postanesthesia visual, auditory, and proprioceptive hallucinations, called emergence phenomena, is more of a concern when ketamine is used as a conscious sedative in painful procedures than in RSI. This effect can be blunted with concomitant use of a benzodiazepine. Of note, emergence phenomena are rare in children, and rates as high as 30% have been reported in adults. Various degrees of hypertonus and skeletal-muscle movement are also occasionally observed.

Thiopental and methohexital

The barbiturates thiopental and methohexital, although used more frequently in the past, have a limited role in the ED as induction agents because of their cardiorespiratory depressant activity. Of all the barbiturates, these possess the shortest onset and briefest duration of action, with methohexital ahead of thiopental.

Propofol

Classified as a sedative hypnotic, 2,6-diisopropylphenol (propofol) is relatively new as an induction agent in RSI. It is extremely lipophilic and distributes itself rapidly throughout the brain and other vascular tissues. For this reason, it must be maintained in an emulsion state to remain in solution.

The induction dose is 2 mg/kg, and it produces a dose-dependent and potent depression of consciousness ranging from light sedation to a comatose state. While it lacks any analgesic activity, it does have amnesic properties. Like etomidate, it has an extremely rapid onset within 1 arm-brain circulation time of about 20 seconds and a likewise a short duration of action of 10-15 minutes.

Like thiopental, propofol decreases cerebral metabolism and, consequently, ICP. Unfortunately, propofol is a myocardial depressant, causing a decrease in mean arterial pressure (MAP). This is compounded by the decrease in the systemic vascular resistance it causes. Both of these factors contribute to an overall decrease in oxygen delivery. These adverse cardiovascular effects are greater than those of the barbiturates and are dose-dependent. The role for propofol may be in the need to intubate a patient with a sympathomimetic drug-induced excited delirium or seizures, especially if ongoing sedation with a constant infusion of propofol is likely to be continued in the intensive care unit.

Propofol depresses pharyngeal and laryngeal muscle tone and reflexes more than the other induction agents mentioned. Respiratory depression may also be observed and is dose-dependent. Although these misgivings are serious shortcomings in its use in RSI, the ultrashort onset, brief duration of action, and extreme potency should be acknowledged.

Midazolam

Although this agent has the most rapid onset of all the benzodiazepines, it falls far short in this category compared with other classes of induction agents. Midazolam has the major disadvantage of requiring titration, which is far from feasible in RSI. Also, optimal effects are not observed for 3-5 minutes. This time does not allow the patient to be properly anesthetized if the midazolam is administered immediately before succinylcholine. In fact, studies have shown that patients are awake if midazolam is administered back to back with succinylcholine. Although the standard dose for RSI is 0.1 mg/kg, doses as high as 0.3 mg/kg have not consistently induced true unconsciousness. Midazolam does mildly decrease CPP. Also, minimal cardiovascular and respiratory effect may be observed.

Because of its slow onset and variable potency, midazolam is no longer recommended as a first-line induction agent in RSI. All drugs administered for RSI must possess rapid onset and extreme potency.

Induction Medications

Induction medications are used to produce anesthesia and unconsciousness.[10, 11, 20]

Table 2. Induction Medications (Open Table in a new window)

Drug Name Generic (Trade)	Adult Dose	Onset of Action	Duration of Action	Advantages	Cautions
Etomidate (Amidate)	0.3 mg/kg IV push (normal adult dose about 20 mg)	0.5-1 min	3-5 min	Does not alter hemodynamics or intracranial pressure (ICP); no histamine release; generally does not induce apnea; useful for patients with multiple trauma and hypotension (does not alter systemic BP)	Commonly causes myoclonus; pain upon injection; adrenal suppression (typically no clinical significance with one bolus)[21]; does not suppress sympathetic response to laryngoscopy; nausea; vomiting; lowers seizure threshold; does not provide analgesia
Ketamine (Ketalar)	1-2 mg/kg slow IV push (not to exceed 0.5 mg/kg/min)	0.5-1 min	5-10 min	Bronchodilatory effects advantageous if hypotension or lung disease present (leaves airway and other protective reflexes intact); rarely used in adults; may possess neuroprotective affects and increase CPP	May increase ICP (though lacking evidence showing clinical significance), hallucinations; increases sympathetic tone, potent cerebral vasodilation, cardiovascular stimulation (do not use with ischemic heart disease); emergence delirium common, but more of a concern when used for conscious sedation with painful procedures (approximately 12%) in adults < 65 y
Propofol (Diprivan)	2-3 mg/kg IV push Decrease dose if patient unstable	< 1 min	3-10 min	Provides rapid onset and brief duration; cerebroprotective (decreases ICP); amnestic properties; extremely potent	Causes cardiovascular depression and hypotension; respiratory depression is dose-dependent

Stage 3 - Paralysis

In normal neurotransmission, the neurotransmitter acetylcholine (Ach) is released from the nerve ending into the neuromuscular junction (NMJ). This occurs secondary to propagation of an action potential along the axon, which results in the opening of calcium channels at the nerve terminal. The flux of calcium ions triggers the release of Ach into the NMJ. Ach diffuses across this gap and binds to nicotinic receptors on the muscle cell endplate opposite the site of the neuronal end terminals. Two molecules of Ach are required at each nicotinic receptor in order for the sodium and potassium ion channels to open. After the threshold of the motor endplate is reached, the muscle membrane is depolarized and excitation-contraction coupling is initiated. After binding, Ach is rapidly hydrolyzed by the enzyme acetylcholinesterase at the NMJ, terminating the stimulatory process, and the muscle membrane repolarizes. Paralyzing agents act by interfering with this process at the NMJ.

Neuromuscular blockade (NMB) agents are divided into 2 general classes based on their mechanism of action at the NMJ: depolarizing and nondepolarizing agents. Depolarizing agents mimic the action of Ach by producing depolarization of the postjunctional membrane, acting as a receptor agonists. Nondepolarizing agents are competitive antagonists of Ach and contend for the Ach subunits of the postjunctional glycoprotein receptors. This prevents changes in the permeability of the postjunctional membrane, thereby not allowing depolarization to occur.

Previous studies have shown that emergent intubations without the use of paralytic agents lead to an increase in adverse events. More recently, Walls et al have looked at 8,937 emergency department intubations and found that the likelihood of any associated event was 1.7 times higher with sedation without paralytics compared with RSI.[22]

Administering a paralytic agent without a potent and effective induction agent is inhumane. It is of utmost importance that this induction agent have an onset of action faster than or at least the same as that of the paralytic agent.

Succinylcholine

Succinylcholine was introduced in 1949 and has passed the test of time. To this day, succinylcholine is the only depolarizing agent used for rapid sequence induction. Because of its rapid onset, ultrashort duration of action, and safety, it is the paralytic of choice in almost all cases of rapid sequence induction in adults.

This depolarizing agent works via persistent activation and resultant blockade of the postsynaptic nicotinic acetylcholine receptor at the neuromuscular junction. In contrary, nondepolarizing agents competitively block the binding of acetylcholine at the same postsynaptic receptor.

Structurally, succinylcholine is 2 Ach molecules linked together by methyl groups. This binds and stimulates the Ach receptor on the postsynaptic neuromuscular endplate, causing ion channels to open and sodium influx to occur. Unlike Ach, succinylcholine produces continuous stimulation of the nicotinic receptor, and the endplate membrane remains depolarized with the channel open. The resulting skeletal muscle paralysis occurs because the hydrolysis of succinylcholine is slow compared with Ach. This sustained depolarization renders the postjunctional membrane unable to respond to subsequent release of Ach because rapid fatigue of the muscle occurs. In essence, the endplate and adjacent sarcolemma are refractory to subsequent stimulation. Paralysis proceeds from the small, distal, rapidly moving muscles to the proximal, slowly moving muscles. The diaphragm is one of the last muscles to relax.

Succinylcholine is rapidly hydrolyzed in the serum by the enzyme pseudocholinesterase and, subsequently, only a small amount ever reaches the NMJ. The end metabolites, succinic acid and choline, have no NMB activity. In fact, pseudocholinesterase is not present in the NMJ and exerts its effect systemically before succinylcholine ever reaches the Ach receptor. Once attached to the Ach receptor, succinylcholine is active until it diffuses back into the serum via the large concentration gradient induced by the rapid action of pseudocholinesterase. These biochemical properties are unmatched by any other NMB agent and have made succinylcholine the criterion standard for rapid neuromuscular paralysis in rapid sequence intubation; thus, the efficacy of all other NMB agents are compared with that of succinylcholine.

Succinylcholine is available as a 20-mg/mL solution and can be stored for as long as 3 months at room temperature while maintaining 90% of its original activity (slightly more if protected from light). Therefore, to potentially lessen spontaneous degradation, succinylcholine should be located on an airway cart near the resuscitation bays and not far away in a remote refrigerator. Proper inventory ensures that it does not remain unused longer than 3 months. The

dose is 1.5 mg/kg in adults and 2 mg/kg in children younger than 5 years. Muscle relaxation occurs in just 30 seconds, with total paralysis in 45 seconds. The duration of action is short, lasting 7-10 minutes.

Adverse effects associated with the use of succinylcholine must be understood in order to anticipate the occasional, but severe, complications associated with its use. Succinylcholine may increase serum potassium levels by as much as 0.5 mEq/L. The risk of an exaggerated release is amplified in certain chronic disease states or after the acute phase of certain injuries or conditions. Therefore, its use in the following high-risk conditions should be discouraged:

- Burns over a large surface area
- Multisystem trauma with crush injury
- Spinal cord and other denervating injuries
- Extensive muscle necrosis (eg, those due to large crush injuries)
- Certain myopathies
- Any preexisting hyperkalemia

Of note, chronic renal failure is not a contraindication to succinylcholine use; however, in the patient with potential hyperkalemia, such as the patient who has missed hemodialysis, alternative agents should be considered for neuromuscular paralysis. Extensive crush injuries and burns sustained more than 7 days earlier may produce more pronounced hyperkalemia.

Patients with large strokes or spinal cord injuries are at risk for hyperkalemia starting about one week after the incident until neuronal regeneration or atrophy has completed. Patients with multiple sclerosis (MS) or amyotrophic lateral sclerosis (ALS) have an ongoing risk of hyperkalemia depending on the activity of their disease. Patients with active myopathy are at greatest risk for succinylcholine-induced hyperkalemia. Despite this, cases of fatal and near-fatal hyperkalemic cardiac arrest are rare. Most cases that have been reported occurred in children with undiagnosed myopathies, none of which occurred in the emergency department, and most had concomitant use of halothane.

Furthermore, although the US Food and Drug Administration (FDA) no longer recommends succinylcholine for use in elective pediatric surgery because of undiagnosed myopathies and fear of subsequent hyperkalemia, it still may be used for emergency endotracheal intubation in children. However, dosing should never be repeated if the airway cannot be intubated during the first succinylcholine-induced muscle relaxation period, as bradydysrhythmias and asystole have occurred. In noncritical situations, alternative neuromuscular agents should be considered in children 8 years and younger. The literature does support the use of succinylcholine in the acute setting outside of any known myopathy or a known case of documented or presumed preintubation hyperkalemia.

The larger elevations observed in chronic diseases are thought to be the effects of extrajunctional Ach receptor proliferation that occurs in states of neuronal regeneration. This provides more sites for outward potassium efflux in the presence of succinylcholine.

Bradydysrhythmias may occur and are more common in children than adults. The risk increases if a second dose of succinylcholine is administered. The mechanism is probably the binding of succinylcholine to postganglionic muscarinic receptors, mimicking the normal effect of Ach on the vagus nerve. Because children younger than 7 years are at greatest risk for this, atropine had been considered a standard prophylactic agent at a dose of 0.01 mg/kg in infants and 0.02 mg/kg in older children, not to exceed 1 mg. In a 1995 report, McAuliffe and colleagues looked at the incidence of succinylcholine-induced bradydysrhythmias in children with and without the use of atropine and found a trend toward an increase in nonclinically important dysrhythmias in the atropine group.[23] They concluded that its use is questionable in any age group and that atropine should possibly be administered only if repeat doses of succinylcholine are needed.[23]

Approximately 3 per 10,000 patients, or 0.03% of the general population, have a defective version of plasma pseudocholinesterase, and they cannot metabolize succinylcholine properly. These individuals possess a decrease affinity for the succinylcholine molecule and a decreased ability to hydrolyze it. In the heterozygote, paralysis may last up to twice the expected duration, but in the homozygote, paralysis may persist for several hours. Known pseudocholinesterase deficiency is an absolute contraindication for succinylcholine use. Many drugs have the potential to lower pseudocholinesterase levels.

Of importance in emergency care, patients with cocaine intoxication may experience prolonged muscle paralysis with succinylcholine use. This is because cocaine is metabolized by the plasma pseudocholinesterases, and, in doing so, it acts as a competitive antagonist. Other important agents are the anticholinesterase agents, which include organophosphate and carbamate pesticides, drugs used for myasthenia gravis, such as pyridostigmine, and drugs used for the treatment of Alzheimer's disease, such as tacrine, donepezil, rivastigmine, and galantamine.

The succinylcholine-induced rise in intraocular pressure (IOP) is minimal (3-8 mm Hg). The mechanism for this slight elevation in pressure may be due to tonic contraction of extraocular muscles, choroid vascular dilation, or relaxation of orbital smooth muscle. Of importance, this is significantly less than the elevation caused by coughing, hypoxemia,

or direct laryngoscopy without a paralytic agent. Even a normal blink of the eyelid can increase the IOP by 10-15 mm Hg. No case of intraocular content expulsion has been reported.

Malignant hyperthermia is a rare disorder that has to do with an excessive release of cytosolic calcium by means of an abnormal ryanodine receptor. This occurs in 1 in 15,000 adults and in 1 in 50,000 children. This rare syndrome consists of muscular rigidity, extreme hyperpyrexia, hypoxemia, hypercarbia, rhabdomyolysis, autonomic instability, metabolic acidosis, and disseminated intravascular coagulation (DIC). Aggressive fluid resuscitation and cooling measures are critical. Early recognition by elevation of end tidal CO_2 monitoring or increased airway resistance should prompt early dantrolene infusion, to lessen mortality and morbidity.

Masseter muscle spasm is much more common than malignant hyperthermia, occurring in 0.3-1% of children. This creates a worrisome situation for the practitioner in which strong contraction of all the masseter muscles clench the mandible. Management should be to continue ventilation and administer a nondepolarizing agent. Because of the relationship between this and subsequent development of malignant hyperthermia, the patient's condition and his or her serum electrolyte and creatine kinase levels, and vital signs should be closely monitored for 24 hours.

Of note, a common misconception is that succinylcholine and rocuronium interfere with the pupillary light reflex. While this initially seems intuitive as the pupillary response is mediated in part by ganglionic nicotinic receptors, the ocular pupillary sphincter muscle itself is composed of smooth muscle, and its neuromuscular endplate is populated by muscarinic acetylcholine receptors. Cargo et al have shown that this clinical dogma is not true, and, in critically ill patients, clinicians should not attribute the absence of such a pupillary response to the administration of paralytic agents.[24]

Rocuronium

Although the adverse effects for succinylcholine are extraordinarily rare, concern for such has prompted investigators to search for an alternative in a shorter-acting nondepolarizing NMB agent. Rocuronium is an aminosteroid muscle relaxant structurally related to vecuronium, though it is more lipophilic and consequently is 3 times as rapid as the latter. It possesses the fastest onset of action of all the nondepolarizing NMB agents, close to that of succinylcholine. At a dose of 0.6 mg/kg, its onset is 60-90 seconds. It is also available as a solution, unlike the other nondepolarizing agents, so drug preparation is reduced. Similar to pancuronium, it possesses some vagolytic properties.

Serensen et al studied this offset of action between succinylcholine and rocuronium-sugammadex. Sugammadex is a new antagonist that binds the rocuronium molecules in a 1:1 ratio. The authors found a significantly quicker offset time in the rocuronium-sugammadex group compared with the succinylcholine group (3 min 26 seconds vs 6 min 46 seconds).[25] Though this paralytic reversal agent is currently being used in Europe, upon US adoption, it has the real potential of replacing succinylcholine, as rocuronium would have the benefit of being reversed, thereby allowing the reestablishment of spontaneous ventilations in the difficult-airway patient. No doubt, the safety of RSI could be enhanced with such an "escape drug."

The major disadvantage in its use in RSI is that its duration of action is intermediate, lasting from 30-45 minutes. It has a faster onset of action in infants and children compared to adults, but the time to recovery in infants younger than 10 months is twice as long as that of older children. Of note, techniques such as priming, synergy, and dosing can shorten the onset of action even further. Sparr reported that when 20 mcg/kg of alfentanil was used as an induction agent, good intubation conditions were met at 45 seconds.[12]

Many studies have shown that rocuronium is an effective and safe alternative to succinylcholine in the rare clinical situation when succinylcholine is deemed undesirable. In a 1994 report, Tryba and colleagues compared succinylcholine 1.5 mg/kg and rocuronium 0.6 mg/kg in a double-blind study of RSI and found no difference with regard to intubation conditions at 60 seconds.[26] De Mey and colleagues reported that increasing the normal dose from 0.6 to 0.9 mg/kg almost halves the onset, giving the same onset as succinylcholine (ie, 45 seconds), but the duration of action is consequently prolonged in a dose-dependent manner.[27]

In further support of the quick onset of action of rocuronium, other investigators point out that the onset at the level of the vocal cords may be quicker than published. After it is administered, the NMB of the diaphragm is slower than laryngeal muscles and slowest at the adductor pollicis muscle, which is often attached to standard twitch monitoring devices. Therefore, conditions for intubation at the vocal cord level may be ideal before peripheral paralysis occurs.

Evidence from the literature has demonstrated that rocuronium does satisfy a requirement for an ideal paralytic agent in its use in RSI, which is the possession of a quick onset of action. However, the other criterion that cannot be met is that of a short duration of action.[28] The potential risk lies in the fact that if an airway is not secured, prolonged bag ventilation for 45 minutes may ensue with all the associated inherent negative sequelae, including the inability to ventilate. Only for this reason, rocuronium has not replaced the criterion standard, succinylcholine, in its use in RSI.[28]

Mivacurium

Like rocuronium, this is a newer NMB agent. It is a bisquaternary benzylisoquinolinium compound structurally similar to atracurium. Because of its rapid hydrolysis by plasma cholinesterases, the duration of action (15-20 min) is classified as short, only 2 times as long as succinylcholine. The typical dose is 0.15-3 mg/kg. Because of the ongoing search for alternatives for succinylcholine, interest in mivacurium is increasing. Two drawbacks are that the onset is 2 -2.5 minutes, which is delayed compared to succinylcholine, and that substantial histamine release occurs with rapid intravenous boluses. However, using techniques such as priming and synergism, the onset can be subsequently reduced, possibly making mivacurium more suitable for RSI.

Molbegott and Baker demonstrated that by preceding an intubating dose of mivacurium 0.2 mg/kg with a priming dose of 0.015 mg/kg, the resulting intubation times and conditions are clinically similar to that produced by succinylcholine.[29] Also, increasing the dose shortens the time for maximal blockade to develop. In 1995, Cook and colleagues have shown that, in children, increasing the dose creates an onset time to complete NMB similar to that of succinylcholine. Like rocuronium, mivacurium is a reasonable alternative when succinylcholine is contraindicated. Although attractive, mivacurium falls short in matching succinylcholine in its simplicity, ultrashort onset, and short duration of action.

Pancuronium

Pancuronium is an aminosteroid NMB. Because the time of onset for paralysis is up to 3 minutes and the duration of action is 60 minutes, the role for this drug is mostly limited to postintubation paralysis. The typical dose is 0.1 mg/kg, although increasing the dose has cumulative effects. Pancuronium causes histamine release and possesses vagolytic properties.

Cis-atracurium

Cis- atracurium is a single *cis-cis* isomer of atracurium, which is enzymatically degraded by hydrolysis in the plasma (Hoffman elimination). By isolating the potent *cis-cis* isomer from atracurium, which is a mixture of 10 stereoisomers, the onset of action with this agent is reduced to 2-3 minutes. It also does not cause histamine release in doses used.

Only rocuronium and *cis* -atracurium are classified as pregnancy category B agents; all others are pregnancy category C. The role of *cis* -atracurium is limited to use in pregnancy, in patients with advanced hepatic disease, and in children. Adult doses are 0.15-0.2 mg/kg, and the pediatric dose is 0.1 mg/kg. Like other nondepolarizing agents, its duration of action, up to 75 minutes, is longer than succinylcholine, limiting its use in emergency situations.

Paralytic Agents

Paralytic agents are essential for effective intubation. For rapid sequence induction (RSI), succinylcholine and rocuronium are commonly used.[10, 11, 20]

Table 3. Paralytic Agents (Open Table in a new window)

Drug Name Generic (Trade)	Adult Dose	Onset of Action	Duration of Action	Advantages	Cautions
Succinylcholine (Anectine)	0.3-2 mg/kg IV push (average dose 1.5 mg/kg)	1 min	4-6 min	Depolarizing NMB; drug of choice for emergency pediatric intubation; rapid onset (< 60 s) and brief duration of action; enhances nondepolarizing neuromuscular blocking effects	Increased serum potassium; muscle fasciculation; malignant hyperthermia; cardiac arrest in children with muscular dystrophy; dysrhythmia with multiple doses
Rocuronium (Zemuron)	0.6-1 mg/kg IV push	< 1 min	30-60 min	Nondepolarizing NMBA; minimal effect on hemodynamics; low incidence of histamine release (0.8%)	Duration prolonged with hepatic impairment

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