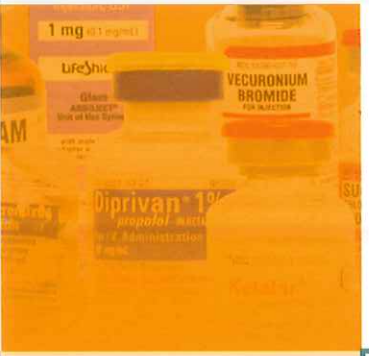


Pharmacology

Chapter 3

Premedication

The sixth "P" of RSI is premedication. Intubation - placing a big piece of metal down someone's throat and then jamming a large plastic tube through their vocal cords - is a noxious procedure to which the body may appropriately respond with tachycardia, hypertension and increased intracranial pressure. The medications used to facilitate RSI may have their own dangerous side effects such as bradycardia or muscle contractions.

Premedications are those medications given before the induction agent and paralytic with the intention of reducing the patient's adverse physiologic responses to the subsequent medications and intubation.

Potential premedications fall into three classes: 1. drugs used to prevent bradycardia, 2. drugs used to prevent bronchospasm, and 3. drugs used to minimize sympathetic outflow/rises in intracranial pressure. All three classes of premedications require at least 3 minutes of circulation time in the body prior to the administration of subsequent medications and/or intubation to be effective; this often limits their usefulness in emergent airway cases. During that 3 minute interval be ready to provide BVMV and intubation; some fragile patients may become apneic from premedications alone.

Caution

Airway911 Consensus: Despite ongoing research and healthy debates, none of the premedications should be considered "Standard-of-care". None are without risk either.

Drugs to Prevent Bradycardia: Atropine

Kids are just one giant Vagus nerve covered in germs! Infants and young children may develop bradycardia during RSI from laryngoscopy, hypoxemia and/or direct medication effects. Infants and children may rarely develop profound bradycardia from propofol or succinylcholine as can anyone, young or old, receiving a second dose of succinylcholine.

It is often recommended that atropine be given "prophylactically" before succinylcholine is administered to any child less than 6 years of age. Some sources recommend atropine to pretreat any infant less than 1 year of age being intubated, regardless if succinylcholine is used. Potential risks of atropine include dysrhythmias and masking hypoxemia. There is very little evidence to support or refute atropine pretreatment. Whether or not it is given prophylactically, atropine should be readily available at the bedside during any pediatric intubation and any time succinylcholine is being used.

Airway911 Consensus: Skip the atropine but have it immediately available. Avoid succinylcholine altogether in kids when possible. If using succinylcholine use large enough doses that re-dosing is never necessary.

Atropine	
Action:	Acts to antagonize vagal stimulation.
Dose:	0.02 mg/kg, minimum of 0.15, maximum of 0.5 mg
Peak:	3 minutes
Duration:	30 minutes
Adverse:	Tachycardia (rare)

Is bradycardia with succinylcholine real or just theoretical?
I have personally witnessed profound bradycardia after succinylcholine in a toddler with a hydrocarbon ingestion; the child started out tachycardic and we were doing chest compressions by the time someone could get the atropine out of the crash cart. Like most cases of succinylcholine-associated bradycardia, this case was complicated by hypoxemia. The literature would suggest these are rare events, however.

Is there any controversy to giving atropine?
Of course! Isn't there some controversy to everything in this business? On one end of the spectrum are experts and guidelines that call for routine use of atropine in any child less than 1 year of age undergoing RSI regardless of the chosen paralytic, children less than 8 years of age getting succinylcholine for RSI, and any age patient getting a second dose of succinylcholine. On the other end are the experts that cite the paucity of evidence that atropine is actually effective in this situation as well as the potential dangers of atropine including tachydysrhythmias and increased risk of aspiration.

Drugs to Prevent Bronchospasm: Lidocaine

In a patient with underlying stable asthma, intubation may provoke bronchospasm which can be mitigated with the use of lidocaine. In a patient being intubated because of their reactive airways disease, i.e. status asthmaticus, intubation may cause worsening of their acute bronchospasm. There are no trials, however, that have looked at this rare population of patients, which is the group we are concerned about for emergent RSI. The best current evidence is therefore limited and somewhat contradictory; it is impossible to make any evidence-based recommendation on the role of lidocaine in this scenario. Pending further research, lidocaine may be considered as a pretreatment for any patient with a history of severe asthma, any patient with detectable wheezing and any patient being intubated for status asthmaticus. Like most pretreatment agents, lidocaine should not be considered standard-of-care.

Airway911 Consensus: use it for unstable asthmatics when time permits.

Lidocaine	
Action:	blunt airway reflex-mediated bronchospasm
Dose:	1.5 mg/kg given 3 minutes before laryngoscopy
Peak:	3 minutes
Duration:	20 minutes
Adverse:	• Hypotension • Allergic Reactions • Seizures • Bradydysrhythmias

Drugs to Minimize Hypertension, Tachycardia and Rises in Intracranial Pressure

Patients with healthy brains tolerate elevations of intracranial pressure (ICP) very well. Consider that your ICP goes up every time you cough or bend over to tie your shoes. Contrast this with patients who have unhealthy brains, particularly ischemic brain tissue or elevated intracranial pressure from head injury or stroke; this is a fragile group at constant risk of secondary injury from anything that decreases perfusion of injured neurons. Rises in ICP adversely effect cerebral perfusion pressure and may, rarely, cause brain herniation.

Caution

Most patients are also tolerant of elevations of blood pressure and heart rate. Many patients undergoing emergent intubation are only alive because their sympathetic flight-or-fight system is kicking in full blast. Occasional patients undergoing RSI, such as those with severe coronary artery disease, may not be so tolerant of tachycardia and hypertension.

Caution

The airway contains a wealth of nerve endings; stimulating these nerves with a laryngoscope may cause elevations of ICP. For this reason a variety of premedications have been advocated to block or blunt these nerve stimulation mediated rises in heart rate, blood pressure and ICP for patients at risk of secondary injury. This includes lidocaine, fentanyl, beta-blockers and defasiculating doses of paralytics. When specifically used in this manner these drugs belong to a class of drugs known as "cerebro-protective" or "cardio-protective" agents".

Lidocaine

Among the most commonly used but least validated cerebral protective premedications is lidocaine. There is little evidence that it produces the desired effects, at least when given intravenously. Lidocaine may be more effective when administered topically in the airway but this is rarely done in the emergency setting for this indication. Moreover there are legitimate concerns about hypotension and allergic reactions. Intubation should never be delayed to give lidocaine if the patient is moribund, combative, or hypoxemic as these conditions are far more dangerous to nervous tissue than the rise in ICP associated with well-performed RSI.

Airway911 Consensus: don't bother.

Lidocaine	
Action:	Anesthetize the airway reflexes that lead to elevated ICP
Dose:	1.5 mg/kg (100 mg in an average adult) 3 minutes prior to laryngoscopy
Peak:	3 minutes
Duration:	20 minutes
Adverse:	• Hypotension • Allergic reactions • Seizures • Bradydysrhythmias

Beta-blockers (Esmolol)

Beta-blockade for cerebral protection and cardiac protection is usually attempted with esmolol (Brevibloc) because it is unique among available beta-blockers: it is administered intravenously, it has a rapid onset and short duration, and it is selective for the *B*1 receptor. Esmolol is among the best-studied and validated agents to blunt the hemodynamic response to intubation though it is unknown if this truly equates to less elevation of ICP. Esmolol is rarely used in emergency settings because of cost and concerns for precipitating hypotension or bronchospasm.

Airway911 Consensus: nice touch for your hypertensive cardiac patients, especially those that have missed routine doses of beta-blockers. Otherwise just say no.

Esmolol	
Action:	Blunts sympathetic response to laryngoscopy
Dose:	1-2 mg/kg 3-5 minutes before laryngoscopy +/- infusion
Peak:	5 minutes
Duration:	10 minutes (heart rate effect shorter and blood pressure effect longer)
Adverse:	• Bradycardia • Hypotension • Bronchospasm

Opiates

High-potency fast-acting synthetic opiates, especially fentanyl, have been evaluated extensively for this indication for over 25 years. The results are not surprisingly contradictory. A non-scientific "meta-analysis" suggests that does over 2 mcg/kg, up to 6 mcg/kg, are most likely to be effective.

Patients with normal-to-high blood pressures, such as most patients with isolated severe head trauma, will rarely become hypotensive from these doses.

Use caution, however, in critically ill and sympathetic-dependent patients, such as severe multi-system trauma. These patients may only be alive because of their sympathetic drive.

Airway911 Consensus: generally safe and provides analgesia if nothing else. Go for 3 mcg/kg if possible.

Fentanyl	
Action:	Analgesic and sympatholytic. Thought to act on ICP through a combination of these two mechanisms.
Dose:	1.5 - 6 mcg/kg 3 minutes before laryngoscopy push slowly
Peak:	3 minutes from end of bolus
Duration:	30 minutes
Adverse:	• Hypotension (primarily if living on their sympathetic drive) • Respiratory depression • Chest wall rigidity - big doses - pushed fast - very young patients

Defasciculating Agents

Fasciculations are chaotic contractions of muscle fibers that may be produced in some adult patients receiving succinylcholine. They are not generally seen in children nor when non-depolarizing paralytics are used. These fasciculations begin in the small muscles of the head and neck and progress towards the lower extremities. These contractions last until paralysis occurs and are thought to contribute to the rise in ICP

seen with succinylcholine. At least one small study of patients in the OR with cerebral pressure monitors demonstrated that blocking fasciculations did minimize the elevation of ICP that occurred following succinylcholine administration.

Many studies have shown that fasciculations may be minimized or eliminated by pretreatment with a small dose of a non-depolarizing paralytic – rocuronium appears to be among the most effective. Succinylcholine has also been evaluated as its own defasciculating agent in small doses but it appears less effective than a non-depolarizing paralytic. The clinical significance of this in acute elevations of ICP is unknown. Effect is time-dependent with up to 5 minutes required for maximal effect. Unfortunately there is also some evidence that the effectiveness of succinylcholine is reduced following pretreatment and dosage may need to be increased.

Airway911 Consensus: On balance, defasciculation does not seem worth the drawbacks and delays and is not recommended. If you are that worried about ICP and you have a non-depolarizing agent available to use for pretreatment, you should probably just use it for the intubation and skip the succinylcholine altogether.

Succinylcholine	
Action:	Block fasciculations
Dose:	0.05 mg/kg 5 minutes before succinylcholine
Peak:	5 minutes
Adverse effects:	• Apnea/hypoventilation • Decreased effectiveness of succinylcholine

Are there any general risks to premedications?

On rare occasions a patient in extremis will become apneic from the premedication, in particular defasiculating doses of paralytics or large doses of fentanyl. You should always have your airway equipment prepared before administration of these medications and monitor the patient carefully. I have seen providers get in trouble when they thought they could use the three minutes it takes for premedications to be effective to prepare their equipment only to find they were totally unprepared for an apneic patient!

So when should I consider these "cerebroprotective" premedications?

These drugs should be considered only if there is a high suspicion of a critically increased intracranial pressure (ICP) and there is time to delay intubation for 3 minutes for the drugs to take effect. If a patient with suspected elevated ICP is combative or hypoxic, delaying intubation for 3 minutes is probably far worse for the patient than the ICP rise associated with intubation without premedications. In such cases, it is likely better to intubate rapidly than wait the three minutes for the medications to have an effect.

So what do you do in practice?

In many cases I do not use any cerebral protective agents. When I have a patient in the ED who is unlikely to tolerate any further rise in ICP, in whom a three minute delay is tolerable and in whom blood pressure is at least high-normal, I will premedicate with fentanyl. A classic example is a patient who returns from CT scanning with an unexpected large intracranial bleed with mid-line shift and deteriorating mental status but no imminent need for intubation. I do not defasciculate since I use rocuronium for paralysis.

Induction Agents

The purpose of an induction agent is to do exactly what you would want done if you were about to have someone paralyze you and stick a tube down your throat: render the patient unconscious and unresponsive. An ideal induction agent should:

- Have a rapid onset and a short duration
- Induce unconsciousness and unresponsiveness
- Provide amnesia
- Have minimal effects on hemodynamics
- Have minimal adverse side effects

Potential induction agents for RSI include etomidate, midazolam, ketamine, propofol, thiopental, and methohexital. The first five agents, the most widely used and available, will be discussed here.

Etomidate (Amidate)

Etomidate is a commonly used induction agent with a generally predictable response and minimal hemodynamic effects; it does not generally raise or lower blood pressure or heart rate. Etomidate may be used in any clinical circumstance including the patient with hypotension or head injury. Seizures have been noted with etomidate, especially in patients with partial seizure disorders, though they are short-lived and this does not represent a significant contraindication for induction. Etomidate is particularly beneficial when increased intracranial pressure is a concern as it has been shown to decrease intracranial pressure, cerebral blood flow and cerebral oxygen metabolism.

The only clinically significant drawback to etomidate is adrenal suppression. There is a great deal of debate in the literature recently regarding this issue, particularly for septic patients. The issue has not been resolved.

The package insert recommends a dose range of 0.2 – 0.6 mg/kg. Most texts suggest 0.3 mg/kg as a standard RSI dose. Dose reduction is often recommended in the hypotensive patient but I have not personally found that to be necessary. On the other hand we have had cases of awareness with 0.3 mg/kg both during induction and during procedural sedation.

Airway911 Consensus: etomidate remains the best single induction agent for RSI. Consider using at least 0.4 mg/kg.

Etomidate	
Dose:	0.2 - 0.4 mg/kg true body weight
Peak:	30 seconds
Duration:	10 minutes
Adverse:	• Adrenal suppression - see below • Myoclonus - not seen when followed by a paralytic during RSI • Vomiting - not seen when followed by a paralytic during RSI • Seizures - not likely clinically significant

So is this adrenal suppression really an issue?

The adrenal glands secrete stress hormones that are incredibly important to critically ill and injured patients. Even a single does of etomidate will suppress the adrenal glands up to 48 hours. In most patients a single dose is probably not clinically significant especially since it may be treated with stress-dose steroid administration. The patients who are most at risk for complications from adrenal suppression, septic shock patients for instance, are the very same patients who require an induction agent that is hemodynamically stable. Suitable alternatives are limited to ketamine which is not widely available. Adrenal suppression is the reason that you cannot use infusions of etomidate for ongoing sedation after intubation; otherwise it would be the perfect drug.

Propofol (Diprivan)

Propofol is beloved for induction of anesthesia in the O.R. and for procedural sedation. Propofol has an extremely rapid onset time and short duration, much like etomidate. Its use in the emergency setting is limited primarily by hypotension. Propofol is considered a cerebroprotective agent as it decreases intracranial pressure and cerebral metabolism though this may be offset by hypotension. It also has antiemetic properties, though this is less important when used with a paralytic as part of RSI. Unlike etomidate, propofol can be used for on-going sedation after the intubation, especially in the hypertensive neurological patient.

Airway911 bottom-line: style points in status epilepticus, isolated neuro patients with hypertension and severe alcohol withdrawal but you can't do anything with this drug that you can't do with etomidate.

Propofol	
Dose:	1 - 2 mg/kg
Onset:	15 - 30 seconds
Duration:	8 minutes
Adverse:	• hypotension • bradycardia

Midazolam (Versed)

Benzodiazepines are common induction agents outside the O.R. though they may not be the best choice for most patients. Benzodiazepines are excellent anterograde and retrograde amnestic agents. This means that patients lose recollection of events that occurred both after and before the drug was given. Benzodiazepines are also excellent anticonvulsant agents and appear to be cerebral-protective agents. They are readily available in most settings, including EMS.

The major problem with these agents is hypotension, especially at induction doses. Dose response can also be quite variable from one patient to another, which can make it difficult to ensure the patient is truly unaware of what is happening. They are also controlled substances, which must be kept secure.

Midazolam is the best of the benzodiazepines for RSI due to its rapid onset and short duration, but it is slower in onset than most other induction agents and should be administered 2 to 3 full minutes before intubation is attempted. This increases the chances that the patient will desaturate and require BVMV and/or be paralyzed before they are fully unaware.

The recommended induction dose for RSI is much higher than the dose used for sedation so high that many providers are uncomfortable giving enough. In clinical practice many patients are induced with low-to-moderate procedural sedation doses. While most patients will still not recall the intubation due to the amnestic effects of the benzodiazepines, would YOU want to be aware? This falls into the "if a tree falls in the forest and nobody hears it, did it really fall?" category of medical practice. Moreover, patients that are aware during the procedure may have dangerous catecholamine responses that raise ICP and stress hearts.

All the benzodiazepines may be used at lower doses for on-going sedation of the intubated patient. While benzodiazepines can be reversed with flumazenil, this is rarely indicated and often dangerous in the emergency setting due to potential seizure activity, particularly in the patient with unrecognized chronic benzodiazepine use.

Airway911 Consensus: skip the benzos for induction if anything else is available.

Midazolam	
Dose:	0.2 - 0.4 mg/kg
Peak:	3 minutes
Duration:	30 minutes
Adverse:	hypotension
Uses:	any non-hypotensive patient though most suited for patients in status epilepticus.

Ketamine (Ketalar)

Ketamine is a dissociative anesthetic agent - the patient may appear to be awake, but is amnestic and unresponsive – often used as part of procedural sedation. Ketamine is used as a surgical anesthetic throughout the developing world due to its excellent safety profile. It is the only induction agent with analgesic properties in addition to sedation. Ketamine is not commonly used as an induction agent in the U.S. but it can be an excellent agent in the hypotensive patient due to catecholamine release. Ketamine may also be a suitable substitute for etomidate in the septic patient. Ketamine is relatively contraindicated in patients with hypertension, coronary artery disease, and/or suspected increased-intracranial pressure (unless hypotensive).

Ketamine increases cardiac output, pulse rate, blood pressure, myocardial oxygen consumption, cerebral blood flow, intracranial pressure and intraocular pressure. While traditionally scorned in the setting of potential neurological injury, ketamine is now being investigated as a cerebro-protective agent. It may be particularly useful in head trauma patients who are hypotensive. Ketamine also increases salivary and bronchial secretions though this is rarely clinically significant. Ketamine may cause emergence reactions but this is not an issue when the patient is to remain intubated and sedated.

Ketamine has been suggested as the preferred induction agent for asthmatic patients. Case reports suggest that induction doses may be effective bronchodilators though recent evidence has challenged the clinical utility of lower doses of ketamine, especially when the patients are simultaneously being treated aggressively with conventional medications. There is insufficient evidence to support routine use of ketamine for asthmatic patients.

Airway911 Consensus: you are likely to see resurgence in use of this old medication for induction, especially for septic patients. Not worth stocking only for this purpose, unless you intubate lots of septic patients.

Ketamine	
Dose:	1.5 mg/kg
Peak:	1 minute
Duration:	15 minutes
Adverse effects:	• HTN • tachycardia • secretions • elevated ICP?
Contraindications:	• HTN • heart disease • pregnancy • age < 3mos • elevated ICP unless hypotensive
Uses:	• Asthma • absolute or relative hypotension • sepsis

Thiopental (Pentothal)

Thiopental is an ultra-short acting barbiturate that has been used as an induction agent forever; the other agents discussed in this section have largely replaced it. The last remaining indication for thiopental is for patients with critical elevations of intracranial pressure and patients with status epilepticus.

Thiopental is a classic cerebroprotective agent. It decreases ICP while also decreasing cerebral oxygen consumption and serving as an anticonvulsant. These benefits are easily offset by potentially disastrous decreases in blood pressure that are particularly common in volume-depleted patients, those with a history of hypertension and those receiving doses at the higher end of the range. Propofol has a very similar risk-benefit profile and is more readily available in most settings. One small advantage to thiopental compared to propofol, especially in children, is the relative lack of burning on injection. Etomidate also has neuroprotective properties with a much better hemodynamic profile than either propofol or thiopental.

Airway911 Consensus: just use propofol or etomidate.

Thiopental	
Dose:	3 mg/kg
Peak:	30 seconds
Duration:	10 minutes
Adverse:	hypotension bronchospasm
Uses:	increased ICP or seizures when blood pressure and volume-status are not an issue

Is it ever appropriate to skip the induction agent?
I have heard of some EMS guidelines that limit RSI to patients with severely depressed mental status and skip the induction agent on the basis that the patient is already unconscious and unaware. I do not personally practice this approach since there is no way to guarantee that the patient is unaware and the risks of awareness are substantial, including catecholamine surge and increased intracranial pressure. The one exception that I occasionally make is the patient with profoundly depressed mental status secondary to overdose with an induction agent such as diazepam. However, it is not inappropriate to give such patients an induction agent if for no other reason than to always be consistent in these critical situations.

Paralytics (Neuromuscular Blockers)

Use of a paralytic is fundamental to the concept of RSI. Recall the definition of RSI from Chapter 1: a series of steps, which must include the administration of a paralytic agent, to a critically ill or injured patient who is presumed to have a full stomach, in order to facilitate rapid successful oral intubation while minimizing complications. The purposes of a paralytic are threefold: 1) to allow intubation in the non-flaccid patient, 2) eliminate muscle tone to optimize laryngoscopy and 3) prevent vomiting. Paralytics should always be used concurrently with an induction agent.

If you elect to paralyze a patient as part of RSI, but you are unable to successfully place the tube and unable to maintain oxygenation through other means the patient may suffer serious harm and/or death. These drugs are wonderful tools but they must be respected for the good they can do and the risks they involve.

There are two general types of paralytics:

1. Depolarizing (non-competitive)
2. Non-depolarizing (competitive)

Depolarizing Agent (Non-Competitive): Succinylcholine (Anectine)

The only clinically available depolarizing neuromuscular blocking agent is succinylcholine. Before we explain the mechanism of action I need to ask any biochemists or pharmacologists or general all-around smarty pants to cover their ears. Thank you on behalf of the rest of us.

Succinylcholine is structurally very similar to acetylcholine - so similar in fact that when succinylcholine binds to acetylcholine receptors at the neuromuscular junction it actually triggers the receptors and stimulates one strong depolarization of the muscle cell. One last hurrah, shall we say? This stimulation of muscle depolarization is seen clinically in many adults as fasciculations; children generally do not have enough muscle mass to demonstrate this.

After the initial depolarization succinylcholine stays locked on the receptor until it is metabolized by pseudocholinesterase, blocking further depolarization and thereby finally producing paralysis. Fortunately the whole process of binding, depolarization and eventual paralysis occurs very quickly. Because succinylcholine fits so well into the acetylcholine receptor and stays so tightly

bound, increasing the amount of acetylcholine in the area of the receptor has no effect on the state of paralysis until the succinylcholine is metabolized. The additional acetylcholine just can't get to the receptors to overcome the state of paralysis. Therefore succinylcholine is considered a "non-competitive" neuromuscular blocker. In practical terms this means that the onset time and duration of action of succinylcholine may be considered independent of dose.

Airway911 Consensus: despite lots of potential adverse effects and complications, succinylcholine has saved tens of thousands of lives, and remains a workhorse for RSI. We find rocuronium to be better a choice overall but many respected experts would disagree.

Succinylcholine	
Action:	depolarizing neuromuscular blockade
Dose:	2 mg/kg true body weight
Peak:	45 seconds
Duration:	8 minutes
Adverse:	see below
Contraindications:	see below

ADVERSE EFFECTS

Succinylcholine may have significant potential side effects, largely related to the depolarization of the muscle cell that occurs. These side effects include:

- **Hyperkalemia:** all patients who receive succinylcholine will have small increases in serum potassium on the order of 0.5 mmol/L. Patients with pre-existing hyperkalemia and those with conditions that cause "up-regulation" of acetylcholine receptors (see table) are at risk for fatal increases in potassium. Succinylcholine should also be used cautiously in dialysis patients whose potassium level is not known, especially if it has been more than 24 hours since their last dialysis. If considered in such patients, intravenous calcium should be immediately available as a potential antidote for cardiac complications.

Conditions that Predispose to Exaggerated Hyperkalemia from Succinylcholine	
Neuromuscular Diseases	**Rhadomyolysis**
Muscular dystrophies	**Burns > 24 to 48 hours old**
Myopathies	**Spinal cord injury > 72 hours and < 9 months old**
Guillian-Barre	**Prolonged immobility/paralysis**
Stroke	**Severe infection (esp. abdominal and neuro)**
Severe Parkinson's	**Severe trauma (esp. muscular)**
Tetanus	
Botulism	

- **Bradycardia:** Bradycardia occurs primarily in children though it can occur in any patient receiving a second dose of succinylcholine. This is one of the reasons to use a larger dose of succinylcholine from the outset lest you get in a situation where you need to give a second dose. Higher dosing also increases your first-pass success and decreases the risk of vomiting; there is little downside to a larger dose with a non-competitive agent.

- **Prolonged paralysis:** Succinylcholine can cause prolonged paralysis in patients who have a deficiency of, or defective, pseudocholinesterase, the enzyme that metabolizes succinylcholine. Several drugs have also been associated with prolonged paralysis, including magnesium, cocaine, lithium, quinidine and cholinergic overdoses. Although confirmed or suspected pseudocholinesterase deficiency is a relative contraindication to the use of succinylcholine, the only complication would be prolongation of the paralysis.

- **Malignant hyperthermia:** This is a very rare but often-fatal condition associated with markedly increased temperature, metabolic acidosis, rhabdomyolysis, and disseminated intravascular coagulopathy. It is most common in patients receiving succinylcholine in combination with inhaled anesthetics in the operating room and extremely rare in other settings. However, if a patient has a known personal or family history of malignant hyperthermia, succinylcholine should not be used.

• **Increased intraocular pressure:** Succinylcholine causes a transient rise in intraocular pressure, which could theoretically cause expulsion of vitreous humor in an open eye injury. I am not aware of any documented case of this complication despite widespread use in open eye surgery. The prudent practitioner will still consider use a non-depolarizing agent in penetrating eye injuries if readily available.

• **Increased intracranial pressure:** Succinylcholine is known to raise ICP transiently. The significance of this rise is not known. The rise is probably due to a combination of the fasciculations and direct medication effects. Succinylcholine is routinely used in the emergency intubation of head-injury patients despite these concerns. Various pre-medications may be considered to minimize these effects in patients for whom even a small increase in ICP may be detrimental (see Premedications).

• **Muscle fasciculations:** Fasciculations are asynchronous contractions of every muscle fiber within a muscle. These fasciculations usually begin in the small muscles of the head and neck and progress towards the larger muscle groups of the lower extremities. They last until paralysis occurs. Fasciculations are thought to contribute to the rise in potassium, ICP and IOP seen with succinylcholine. Fasciculations are not usually seen in children due to their smaller muscle masses.

• **Trismus:** Paradoxical spasm of the Masseter muscle which may make intubation difficult or impossible is a well documented though rare complication of succinylcholine. If it occurs it may be reversed by administering a non-depolarizing neuromuscular blocker. The mechanism of action is not well understood. It certainly makes no sense intuitively that a drug used to cause paralysis could cause muscle spasm. Some reported cases may have been due to ineffective vials of medication or dosing and administration errors such as infiltrated lines and forgotten tourniquets. Don't let that happen to you.

CONTRAINDICATIONS

Caution

Because of the potential adverse effects listed above, especially hyperkalemia, succinylcholine is relatively contraindicated in a number of conditions including, but not limited to:

- Personal or family history of malignant hyperthermia
- Neuromuscular diseases
- Known or suspected hyperkalemia
- Crush injury/Rhadomyolysis
- Burns > 24 to 48 hours old
- Spinal cord injury > 72 hours and < 9 months old
- Increased intracranial pressure
- Orbital injury
- Prolonged immobility/paralysis
- Severe infection (esp. abdominal and neuro)
- Severe trauma (esp. muscle trauma)

Where do you come up with these big doses of succinylcholine?
It's true that some sources recommend dosages as low as 0.5 mg/kg. I obviously disagree. I have seen many patients in whom 1 mg/kg was clearly not enough to achieve adequate paralysis. In emergency situations we cannot afford the risks of inadequate dosing on the first attempt: aspiration from placing a laryngoscope into the mouth of a "half-paralyzed" patient, time delays to give a second dose often resulting in the need for BVMV to maintain oxygen saturations, and the risk of bradycardia with a second dose. I have personally observed each of these complications. On the flip side, what does an "overdose" of succinylcholine look like? It looks exactly like what you are aiming for: paralysis. Because succinylcholine is a non-depolarizing agent, side effects and duration do not change dramatically with a larger dose. So why aim low???

Can succinylcholine be used intramuscular (IM)?
Yes, succinylcholine has been used IM at doses of about 4 mg/kg. The onset time is about 4 minutes in a well-perfused patient; probably longer in patients needing emergent RSI. With the widespread availability of adult and pediatric intraosseous devices this should almost never be necessary. As an alternative, I have given succinylcholine directly into the femoral vein – "main-lined" - in a few extreme situations.

Non-depolarizing (Competitive) Agents

The other class of paralytics are the non-depolarizing agents such as vecuronium (Norcuron), pancuronium (Pavulon), cisatracurium (Nimbex) and rocuronium (Zemuron) among others. These agents also bind to the acetylcholine receptors in the neuromuscular junction but because they do not share the structural similarity with acetylcholine that succinylcholine does - "vecuronium" doesn't sound much like "acetylcholine" - they do not stimulate the receptor. Hence these agents are "non-depolarizing" and they do not produce fasciculations. This would be another good time for the PhD and PharmD types to tune out...

Since the non-depolarizing agents do not fit into the receptors well they do not stay tightly bound like succinylcholine; instead they bind, fall-off and rebind constantly. Each time the drug releases from the receptor there is a "race" between acetylcholine and the remaining drug to see which will bind to the open receptor next. If the drug wins then paralysis is maintained and if acetylcholine wins the paralysis wanes. If the concentration of drug in the synapse is increased, the chances that the drug will make it past a paralytic molecule to the receptor are increased, and vice-versa. Therefore these are considered "competitive" agents.

The clinical significance of this competition is that the speed of onset and duration of all drugs in this class is dose-dependent. If a larger dose is administered the drug will out-compete the acetylcholine sooner (faster onset) and for a longer period of time (longer duration). Anesthesiologists and anesthetists may take advantage of this competition in the O.R. to "reverse" the paralysis by administering agents that increase the amount of acetylcholine in the synapse. Unfortunately, this only works once about 75% of paralysis has waned by metabolism. Therefore it is not very useful in the emergency setting.

The major clinical advantage to the non-depolarizing agents outside of the O.R. is the relative paucity of adverse effects and contraindications. Not only does this add potential safety but also the RSI sequence is simplified by the absence of most pre-medications. Atropine is not indicated as these drugs do not induce bradycardia. Defasiculation is not indicated as these drugs do not induce fasciculations. Lidocaine, beta-blockers and fentanyl are less important because the non-depolarizing agents do not have the inherent potential to raise ICP like succinylcholine.

Traditionally the major drawback to the competitive agents has been a prolonged onset time and duration. Now some of the newer agents such as rocuronium have an onset time comparable to succinylcholine. The longer duration of action is less clinically important now that we have excellent extraglottic airways and practice "three strike and you're out" intubation. Previously, when the only back-up airway was a cricothyroidotomy, there was safety in being able to let succinylcholine wear off. Today, we move to back-up airways long before even short-acting agents like succinylcholine wear off. Many emergency physicians, critical care specialists, pediatricians and flight programs now favor these agents over succinylcholine for RSI. These agents have always been used for maintenance of paralysis in the intubated patient.

Rocuronium (Zemuron)

Rocuronium is a non-polarizing neuromuscular blocker. The published dose range is from 0.6 to 1.2 mg/kg. Doses at the higher end of the range are necssary in emergency situations to improve intubating conditions and reduce onset time to near 1 minute (remember, this is a non-depolarizing and therefore competitive agent). Rocuronium is commonly used to replace succinylcholine for RSI as long as the greater duration of action is acceptable.

It may also be used to maintain paralysis after RSI. Many clinicians prefer rocuronium, especially for pediatric patients, as you can use one drug for RSI and maintenance, there is less reason to consider premedication and it has few adverse effects and contraindications:

- No bradycardia
- No increased ICP/IOP
- No fasciculations
- No hyperkalemia
- No malignant hyperthermia

The slightly longer onset time (15 seconds or so) is rarely clinically significant and can be overcome if necessary by giving the rocuronium before the induction agent: the timing principle. However, in most patients, the traditional order of induction agent then paralytic works fine with rocuronium.

Airway911 bottom-line: Love it! We use it virtually exclusively both in the hospital and air medical setting.

Rocuronium	
Action:	non-depolarizing neuromuscular blocker
Dose:	1 mg/kg ideal body weight
Peak:	60 seconds
Duration:	30 minutes
Adverse:	Usually minimal. Anaphylaxis has been reported rarely.

Is rocuronium safe to replace succinylcholine for RSI?

The primary argument against rocuronium has been its long duration, especially at the higher suggested intubation dosages. This argument is a holdover from the days when the only back-up airway was a surgical airway. Today, we have excellent back-up extraglottic devices and we would rarely if ever consider waiting for even a short-acting paralytic like succinylcholine to wear off before placing one. For an elective case in the O.R., where there may be an option of letting the paralytic wear off and rescheduling the case, it may make some sense to choose a shorter acting paralytic for difficult intubations. In the emergency setting this is rarely a good option: if the patient did not mandate intubation RSI would not have been undertaken in the first place. Our patients require airway management one way or another so the duration of action is not that important. Overall, rocuronium is an excellent drug for emergent RSI if used appropriately. It is widely used for this indication.

Wasn't rocuronium recently blasted by the Cochrane Collaboration?

It is true that rocuronium was recently blasted in a Cochrane Collaboration review but close reading reveals that most studies reviewed used dosages on the low end of the range. It is no surprise with a competitive neuromuscular blocker that results would be poor with lower doses. They go on to state that "We found no statistical difference in intubating conditions when succinylcholine was compared to 1.2 mg/kg rocuronium..." So there!

Vecuronium

Vecuronium is a non-depolarizing neuromuscular blocker which is no longer commonly used for RSI. A dose of 0.15 mg/kg persists for about 30 minutes. Onset is typically 2 – 3 minutes, but can be reduced to at best 90 seconds by increasing the dose up to 0.3 mg/kg and/or using the timing and priming principles discussed below. The chances of a patient needing interposed BVMV are higher with vecuronium than other available paralytics. At a dose of 0.3 mg/kg the paralytic effect will persist over one hour.

Caution

The timing principle simply dictates that you administer the dose of paralytic first and wait to give the induction agent until the onset time of the two drugs will be the same. For instance, if you are using etomidate which has a 30-second onset time and standard-dose vecuronium which has an onset time of approximately 2.5 minutes you would give the paralytic first and wait 2 minutes to give the etomidate. Both drugs would then take effect at more or less the same time--or 2.5 minutes from beginning. Unfortunately, the paralytic effect phases in gradually rather than suddenly, so the patient could be sufficiently paralyzed to be extremely distressed before the 2.5-minute mark.

Caution

The priming principle calls for the administration of a small dose of vecuronium in advance of the intubating dose, similar to defasciculation. Unfortunately it creates some confusion and produces onset and duration times similar to simple high-dose vecuronium.

In the emergency setting vecuronium is primarily used at standard dosing to maintain paralysis after RSI.

Airway911 bottom-line: Say no if possible. If vecuronium is the only agent available for RSI, use 0.3 mg/kg and a modified timing principle: give the vecuronium first but follow immediately with the induction agent. Be prepared for careful BVMV.

Vecuronium	
Regular Dose:	0.15 mg/kg
High-dose:	0.3 mg/kg
Peak:	90 seconds (high-dose) 3 minutes (regular-dose)
Duration:	30 - 90 minutes (dose dependent)
Adverse:	Minimal
Adverse:	Minimal

Sugammadex

Sugammadex is a new drug that will reverse paralysis from intubating dosages of rocuronium (and vecuronium to a slightly less extent) within 2 minutes. Sugammedex works by encapsulating the rocuronium molecules. The drug is approved in Europe but was rejected by the FDA in August 2008 due to concerns about hypersensitivity reactions. If the experience in Europe is favorable it will likely gain approval in the United States but may be very expensive.

It is unclear how the availability of a drug to reverse rocuronium would affect emergency airway management. Those who believe a short-acting agent provides a significant safety margin may finally be convinced to switch from succinylcholine to rocuronium. Those who already believe rocuronium is safe for RSI and practice based on moving to plan B in the event of difficulty even before 2 minutes have passed may not find much benefit.

Airway911 Consensus: let's wait and see if it becomes available and how much it costs.

Sedatives & Analgesics

Sedatives

The purpose of sedation is to alleviate the anxiety of paralysis and intubation and to produce amnesia. A patient must never be given paralytics without adequate sedation. The primary sedative agents after RSI are the benzodiazepines of which midazolam is probably the most common; diazepam and lorazepam are also acceptable. Propofol may also be considered for emergency use, especially for patients with isolated neurological conditions. Occasionally a patient will be too hypotensive to tolerate benzodiazepines; ketamine may be an effective sedative in this situation.

Analgesics

The purpose of an analgesic as part of RSI is to combat pain both from the pre-existing conditions associated with the need for intubation (major trauma or myocardial infarction with cardiogenic shock for example) and from the intubation itself. Fentanyl is commonly used because of its rapid onset, minimal side-effects, and widespread availability.

Fentanyl (Sublimaze)

Fentanyl is a rapid-acting synthetic opiate of relatively short duration. At appropriate does it produes peak analgesia within 2 to 3 minutes, with an effective duration of about 30 minutes. It does not have significant sedative properties in adults. In young children it may have profound sedative effects, which may allow it to be used for both post-intubation analgesia and sedation. Fentanyl is well tolerated by most patients with little hypotension seen except in the most fragile, sympathetic dependent, patients. Fentanyl may be administered in boluses or by infusion.

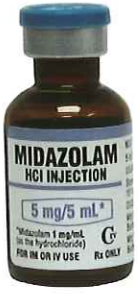
Fentanyl	
Bolus Dose:	Adults: 25 - 100 micrograms every 3 - 5 minutes as needed Children: 1 - 2 micrograms/kg every 3 - 5 as needed
Infusion:	Adults: 100 - 500 micograms/hour Children: 2 - 5 micrograms/kg/hour
Peak:	3 minutes
Duration:	30 minutes
Adverse:	• Hypotension (primarily if living on their sympathetic drive) • Chest wall rigidity - big doses - pushed fast - very young patients

I hear that fentanyl does not cause hypotension but I swear I've seen it. Is that possible?

Yes! It is true that fentanyl usually does not cause hypotension compared to other narcotics such as morphine sulfate. However, in addition to being a potent analgesic, fentanyl is a sympatholytic agent which means it blocks sympathetic outflow. Some critically ill patients are only alive because of an exaggerated sympathetic "fight-or-flight" response. Fentanyl may block this compensatory response and cause hypotension or vascular collapse; it should be used very cautiously in such patients.

Midazolam (Versed)

Midazolam is probably the most commonly used sedative for recently intubated patients in most settings, particularly in the ED and during critical care transport. It is preferred because of its rapid onset and short duration making for easy titration. Midazolam also provides excellent amnesia. It may be administered by bolus or infusion.



The major limitation to midazolam for post-intubation sedation is hypotension. This effect is most pronounced in volume-depleted patients, the elderly and/or those concurrently receiving narcotics. Dosage should be reduced in these groups. Some critically ill patients may be too hypotensive to tolerate even small doses of midazolam. Pregnancy class D.

Midazolam	
Bolus Dose:	Adults: 1 - 5 mg every 3 - 5 minutes as needed Children: 0.05 - 0.1 mg/kg up every 3 - 5 minutes as needed
Infusion Dose:	Adults: 5 - 10 mg/hr Children: 0.1 - 0.2 mg/kg/hr
Peak:	3 minutes
Duration:	20 - 30 minutes
Adverse effect:	hypotension
Uses:	any non-pregnant patient unless hypotensive

Ketamine (Ketalar)

Ketamine is a unique dissociative sedative with profound analgesic properties as well. Ketamine is most commonly used for procedural sedation, especially in children, though it can also be used as a general anesthetic, induction agent and sedative/analgesic for intubated patients. This latter use is surprisingly uncommon given that ketamine is the only strong sedative/analgesic that does not cause hypotension. In fact, ketamine will often raise blood pressure. It may be administered by bolus or infusion.

Caution

Ketamine is absolutely contraindicated in patients with hypertension and relatively contraindicated in coronary artery disease and elevated intracranial pressure. As discussed above, concerns regarding ketamine and ICP are now being debunked.

Ketamine	
Dose:	0.25 - 1 mg/kg every 3 - 5 minutes as needed
Peak:	1 minute
Duration:	15 minutes
Adverse effect:	• hypertension • tachycardia • oral secretions • elevated ICP?
contraindications:	• Hypertension • Heart disease • Pregnancy (class X) • Age less than 3 months • Elevated ICP - unless hypotensive
Uses:	• asthma • hypotension ▪ absolute or relative • septic shock

Propofol (Diprivan)

Propofol is a unique sedative agent. It is commonly used in the O.R. setting as an induction agent and in the O.R. and ICU settings as a sedative for intubated patients. Propofol is also used for procedural sedation. Propofol has the advantage of rapid onset and short duration of action. In fact, propofol infusion may be turned off and the patient's neurologic status rapidly assessed. This is extremely beneficial in patients with underlying neurological conditions such as stroke, head trauma

and seizures. Propofol is an anti-convulsant and also highly effective in alcohol withdrawal. It may be administered by bolus or infusion but is most common as an infusion.

The major limitation to propofol as a sedative for intubated patients is the associated hypotension. This may be particularly marked in the volume-depleted patient. For this reason propofol is not recommended for trauma patients in whom internal bleeding has not be effectively ruled-out or patients with signs of sepsis or cardiogenic shock. Administration by infusion generally results in less hypotension than bolus administration.

Propofol	
Bolus Dose:	0.25 to 0.5 mg/kg every minute as needed
Infusion dosing:	0.5 - 5 mg/kg/hr
Peak:	1 minute
Duration:	20 - 30 minutes
Adverse effect:	• hypotension • Bradycardia
Uses:	• neurotrauma • stroke • seizures • alcohol withdrawal • pregnancy

Etomidate seems like the perfect drug for post-intubation sedation. Why do I never see it used that way?
While its hemodynamic stability is unparalleled, the problem with etomidate is suppression of the adrenal glands, which are critical in the body's response to stressors such as major illness or injury. Etomidate must NEVER be used for ongoing sedation; only a single dose for RSI is acceptable.

Do you ever give medications during the airway procedure?

Yes. If you are using a short-acting induction agent and/or paralytic such as etomidate and succinylcholine you may need to give additional doses in the event that the airway procedure is longer than usual, i.e. difficulties are encountered. Second doses of succinylcholine are associated with bradycardia in any age patient and additional doses of etomidate increase the risk of adrenal suppression. I usually use rocuronium, a long-acting paralytic, so I rarely need to give additional doses until well after the procedure. However, I will often give a dose of fentanyl and midazolam (blood pressure permitting) during a long procedure to be sure that the patient is comfortable.

What is "PISA"?

"PISA" stands for "paralyze, induce, sedate and analgese". This is a new approach that attempts to minimize the time that a recently intubated patient goes without analgesia and sedation in emergency situations. The usual practice is to give premedications, then give an induction agent and paralytic, perform the intubation, confirm the tube and then draw up and administer the sedation and analgesia. In chaotic environments and/or if there are a limited number of hands (i.e. a flight crew in the aircraft) this can result in unacceptable delays to give the sedation and analgesia; delays in which the patient is often extremely anxious and uncomfortable resulting in increased blood pressure, heart rate and ICP. When using the PISA approach, premedications are generally not administered as the rocuronium is used as the paralytic. Rocuronium is given immediately before the etomidate taking advantage of the more rapid onset of etomidate. The first dose of analgesia and sedation is given at the same time as the induction agent and paralytic, before the intubation. Additional analgesia and sedation should still be titrated as soon as possible after the tube is confirmed.

Take Home Points

- Premedications are those medications given before the induction agent and paralytic with the intention of reducing the patient's adverse physiologic responses to the subsequent medications and intubation
  1. None of the premedications are "standard-of-care"
  2. All require at least 3 minutes to work
  3. Consider fentanyl in the setting of elevated ICP or coronary artery disease and lidocaine for patients with asthma

- Induction agents make the patient unaware of the impending intubation
  1. Etomidate is the overall safest agent for most emergency situations
  2. Consider ketamine as an alternative for septic patients

- Paralytics permit laryngoscopy, eliminate muscle tone and prevent the patient from actively vomiting
  1. There are two categories of paralytics:
     - Depolarizing/non-competitive (succinylcholine)
       - Dose-independent onset and duration
       - Multiple though rare adverse effects and contraindications
     - Non-depolarizing /competitive (rocuronium, vecuronium, others)
       - Dose-dependent onset and duration
       - Few adverse effects and contraindications

- All chemically paralyzed and/or recently intubated patients should receive immediate and frequent analgesia and sedation
  1. Midazolam with fentanyl most common
     - Adjust for blood pressure
  2. Consider propofol in isolated neuro patients with hypertension
  3. Consider ketamine if hypotensive

Case Scenario

Neuro Case

A 68-year old woman with history of 3-vessel CABG and 1-vessel stenting presents to a rural ED with a severe headache with vomiting for 2 hours. She also has a history of rheumatoid arthritis. She has dentures. She has not taken any of her routine medications including her metoprolol today. Her mental status is normal and her neuro exam is non-focal. Her blood pressure is 220/160, heart rate 86, respirations 20 and saturation 95% on room air. She is taken to CT scanning where a large subarachnoid hemorrhage is detected. On return from the scanner her mental status is noted to have dropped to GCS 12. The accepting neurosurgeon recommends intubation prior to critical care ground transport to a neurosurgical referral center. What is your assessment and plan?

This patient has an unclipped aneurysm as well as severe CAD and great care has to be taken not to elevate her ICP or blood pressure too much. The airway may be complicated by limited neck mobility but that will probably be offset by removing her dentures for the intubation.

LEMONS: Neck mobility may be limited by her rheumatoid arthritis and this should be assessed before proceeding. Unless severe this will probably be offset by removing her dentures for the intubation.

PREOXYGENATE: Use non-rebreather mask on high-flow oxygen.

PROTECT C-SPINE: Not indicated.

PRESSURE TO CRICOID: Will be used, but very gently, from the time induction medication is given until the tube is confirmed in the trachea, unless the intubation proves difficult.

PONDER: This is NOT a crash airway. There is no reason not to take enough time to do it calmly and correctly. There is plenty of time to call for assistance if you anticipate difficulty. The primary alternative is to defer intubation but that has already been discussed with the neurosurgeon. It is important that the neurosurgeon be informed of any anticipated difficulties with intubation so they can factor that into the risk-benefit analysis. The back-up will be any appropriately sized EAD.

PREPARE EQUIPMENT AND PEOPLE: I would have at least two sizes of cuffed endotracheal tubes available. I would also have a bougie and two sizes of EAD available though they probably do not need to be taken out of the package. I would have both straight and curved laryngoscope blades available. Assistants prepared to monitor saturations, assist with cricoid pressure/ELM, assist with the bougie and hold the tube will be very important so the intubator can stay focused on the airway.

PREMEDICATE: I would give the patient a small fluid bolus to make sure her tank is full and then premedicate with esmolol 1 mg/kg 5 minutes before intubation and fentanyl 3 micrograms/kg 3 minutes before intubation.

POSITION THE PATIENT OPTIMALLY: There should be time to insure a perfect sniffing position.

PARALYZE AND INDUCE: I would induce with etomidate as I would be fearful of hypotension combining esmolol and fentanyl with propofol or midazolam. I would paralyze with rocuronium to avoid any additional risk of elevated ICP from fasciculations.

PASS THE TUBE: The dentures would be left in-place until just before the intubation in case BVMV were required. They would be replaced if BVMV became necessary for a missed intubation.

POST-INTUBATION MANAGEMENT: Immediately after the tube is confirmed it will be secured and the patient placed on the ventilator with continuous capnography. The patient will receive fentanyl for analgesia and, if her blood pressure remains elevated, propofol for sedation. Further blood pressure management will be discussed with the neurosurgeon and flight team.