Overview of Pharmacology of Rapid Sequence Intubation & Post-Sedation Analgesia in the Emergency Department

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Disclosures

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Objectives Pharmacists & Nurses

- Review medications commonly used for rapid sequence intubation
- Identify the components of post-intubation management
- Describe agents used in post-intubation management for analgesia and sedation

Objectives Pharmacy Technicians

- Review medications commonly used for rapid sequence intubation
- Identify the importance of timely access to medications used for post-intubation management
- Describe storage and strategies for safe utilization of medications used for post-intubation management

Rapid Sequence Intubation (RSI) overview

- Rapid sequence intubation is a process of providing rapid administration of a general anesthetic (induction) or sedative to create a state of unconsciousness with a neuromuscular blocking agent (NMBA) also known as a paralytic agent for facilitating endotracheal intubation

- Purpose is to make the emergent intubation easier and safer to increase success rates of intubation (first pass success) and decrease complications

- Intubation is the process of securing an airway in patients who are unable to maintain an airway or who cannot breathe on their own

Source: Hampton JP. *Am J Health System Pharm*. 2011

Steps of RSI focusing on pharmacology

Preparation

Pre-oxygenation

Pre-Treatment

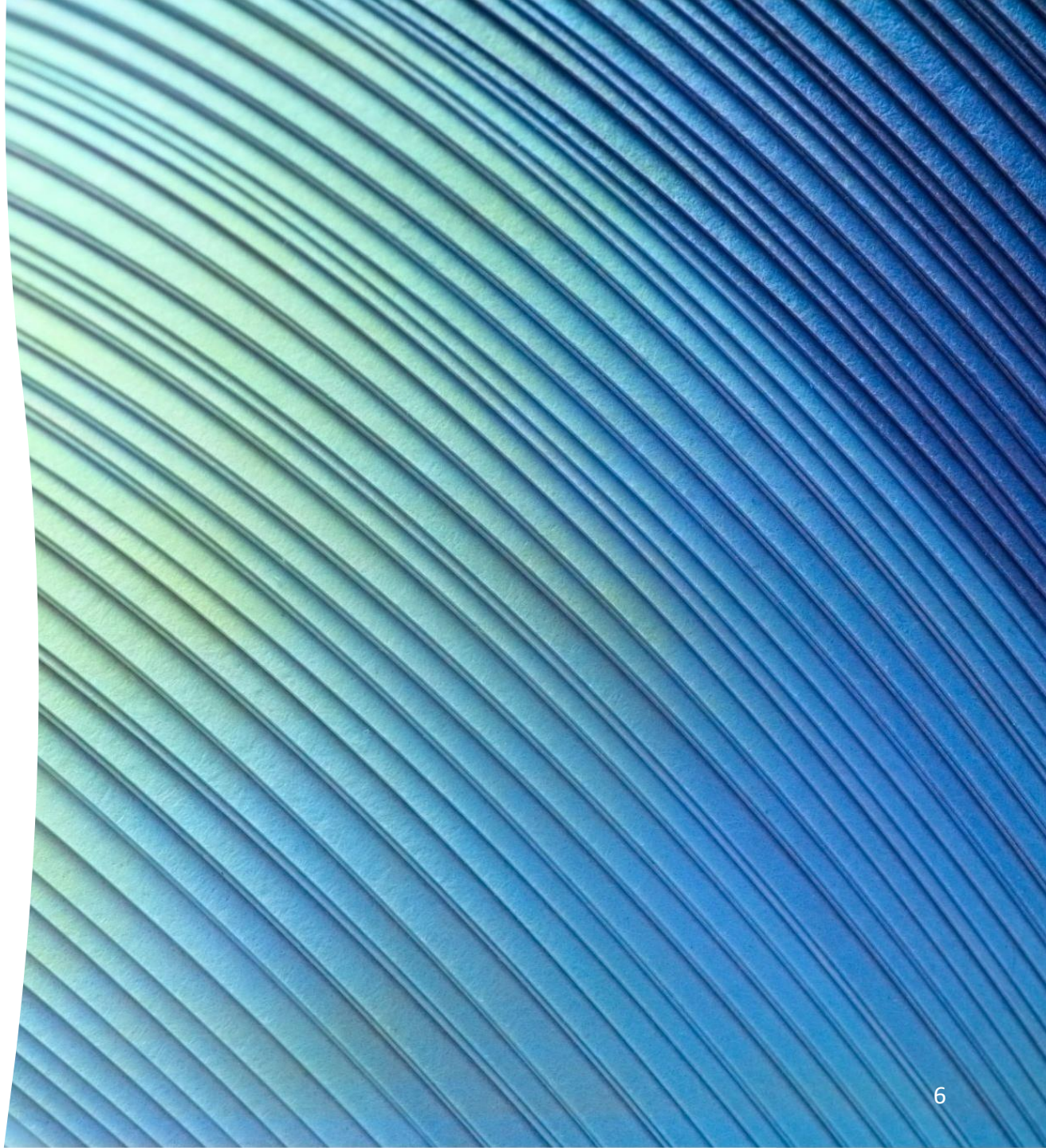
Paralysis with induction

Protection/Positioning

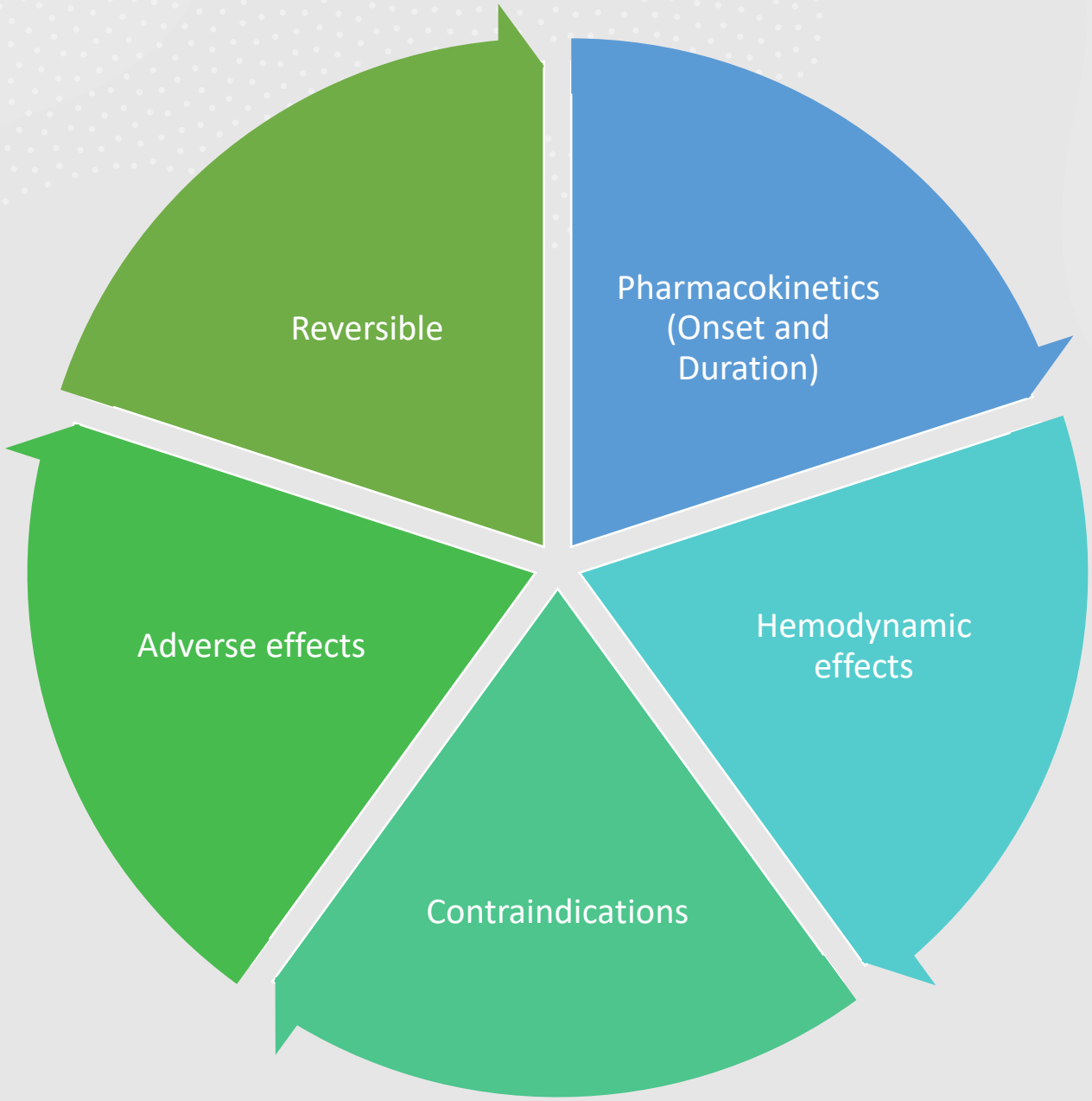
Placement with proof

Post intubation management

Source: Hampton JP. *Am J Health System Pharm*. 2011



Medication Considerations



Source: Hampton JP. *Am J Health System Pharm*. 2011

Preparation

- Obtain all necessary equipment and patient weight
- Obtain medications needed for pre-treatment, induction, paralysis, and post-intubation sedation and analgesia
- Confirm any needed laboratory values, allergies or past medical history if available
- Ensure all appropriate personnel are available
- Checklist if appropriate

Sources: Caruso M.C., et al. *Am J Health System Pharm*. 2017.
Hampton JP. *Am J Health System Pharm*. 2011.

Pre-Treatment

- Purpose: Attenuate the pathophysiological response to laryngoscopy and intubation

- Pathophysiology:
  - ✓Sympathetic and parasympathetic nerves when stimulated can release catecholamines
    - ➢Increases in heart rate (30 beats per minute) or mean arterial pressure (MAP) by 20 mmHg
  - ✓Placement of the endotracheal tube stimulates upper airway reflexes
    - ➢Bronchospasms, laryngospasms, cough
    - ➢Increases in intracranial pressure (ICP)

- Administer medications 3 minutes prior to administration of paralytics and induction agents

- Historically known as “LOAD”
  - ✓Lidocaine, opioids (fentanyl), atropine, defasciculating doses of paralytics
    - ➢Consider atropine for bradycardic in patients over the age of 1 year
    - ➢Consider midazolam for anxiolysis

Sources: Hampton JP. Am J Health System Pharm. 2011.
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Pre-Treatment

Characteristics	Lidocaine	Fentanyl	Atropine	Midazolam
Mechanism	Class 1B antiarrhythmic Sodium channel blocker	Opioid-receptor agonist	Antagonist of muscarinic receptors in the parasympathetic nervous system	Agonist of GABA receptors
Use for Pre-Treatment	Decreases sympathetic response to intubation, inhibits cough reflex and bronchospasm	Provides analgesia associated with intubation; prevents catecholamine release	Blunts vagal response	For anxiolysis
Dosing	1.5 mg/kg intravenous push (IVP) over 2 min	1-3 mcg/kg IVP over 30-60 seconds	0.01 mg/kg IVP over 30 seconds	1-2 mg IVP or intramuscular (IM) over 60-90 seconds
Onset/Duration	Onset: 45-90 seconds Duration: 10-20 minutes	Onset: Immediate Duration: 1 hour	Onset: 2-16 minutes Duration: 3 hours	Onset: 60-90 seconds Duration: 1-4 hours
Comments	Contraindications: Bradycardia, heart block, amide anesthetic allergy	Administration: Chest wall rigidity May cause respiratory depression	May be beneficial in patients with bradycardia or significant amount of secretions	May cause respiratory depression

Sources: Hampton JP. Am J Health System Pharm. 2011.
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Induction Agents and Overview

- Purpose: Induce unconsciousness rapidly with induction agents followed by paralysis with NMBA to promote increased rates of first success intubation
- Goal of induction is to create general anesthesia state and cause retrograde amnesia

Induction Agents	Pharmacokinetics: Onset/Duration	Pharmacokinetics: Elimination
Etomidate	Onset: 5-30 seconds Duration: 5-15 minutes	Elimination: Hydrolysis in the liver and plasma esterases to inactive metabolites, renally eliminated (75%) Half life: 2.5-3.5 hours
Ketamine	Onset: 30-60 seconds Duration: 5-15 minutes	Eliminated: Hepatic enzymes into inactive metabolites and renally eliminated Half life: 10 minutes-2.5 hours
Midazolam	Onset: 60-150 seconds Duration: 30-80 minutes	Elimination: Hepatic enzymes into metabolites (60-70%) and renally eliminated (90%) Half life: 3 hours
Propofol	Onset: 10-60 seconds Duration: 3-10 minutes	Elimination: urine (88%) as metabolites Half life: 40 minutes

Sources: Hampton JP. Am J Health System Pharm. 2011.
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Induction: Etomidate

- Mechanism: Benzyl-imidazole, non-barbiturate ultra rapid hypnotic agent
  - ✓No analgesia or amnesia properties
- Dosing: 0.3 mg/kg IVP
- Considerations and adverse effects
  - ✓Predictable pharmacokinetics, hemodynamically neutral, no histamine release
  - ✓Contraindications: adrenal insufficiency (e.g. sepsis)
  - ✓Adverse effects: Injection site reaction (30-80%), myoclonic movements (80% without neuromuscular blocking agent or sedative), hiccups (30%), vomiting (40%)
- Availability
  - ✓2mg/mL 10mL or 20mL vials
- Storage
  - ✓Store at room temperature: 20°C to 25ºC (68°F to 77ºF)

Sources: Hampton JP. *Am J Health System Pharm* 2011.
Cherfan AJ, et al *Pharmacotherapy* 2012.
Ray DC, et al. *Crit Care* 2007.
Elliot M, et al. *Can J Hosp Pharm 2012.*
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Induction: Ketamine

- Mechanism: non-competitive N-Methyl-D-aspartic acid (NMDA) receptor antagonist, weak opioid receptor agonist
  - ✓Provides analgesia and amnesia
- Dosing: 1-2 mg/kg IVP over 30-60 seconds
- Considerations and adverse effects
  - ✓Increase hemodynamics (mean arterial pressure, heart rate, intracranial pressure)
  - ✓Contraindications: Schizophrenia
  - ✓Adverse effects: prolonged emergence (10%) reactions such as confusion, delirium, and hallucinations
- Availability
  - ✓10 mg/mL (20mL), 50 mg/mL (10mL), 100 mg/mL (5mL)
- Storage
  - ✓Schedule III substance
  - ✓Store at room temperature: 20°C to 25ºC (68°F to 77ºF)

Source: Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Induction: Midazolam

- Mechanism: Benzodiazepine, binds to gamma-aminobutyric acid (GABA)
  - ✓Provides amnesia, anxiolysis, muscle relaxant, hypnosis
- Dosing: 0.1-0.3 mg/kg IVP
- Considerations and adverse effects
  - ✓Adverse effects: Respiratory depression, hypotension, hypoxia, sedation, paradoxical agitation
- Availability
  - ✓2mg/2mL or 5mg/5mL
- Storage
  - ✓Schedule IV substance
  - ✓Store at room temperature: 20°C to 25ºC (68°F to 77ºF)

Source: Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Induction: Propofol

- Mechanism: Non-benzodiazepine with GABA activity
  - ✓Provides amnesia
- Dosing: 1.5-2.5mg/kg IVP
- Considerations and adverse effects
  - ✓Beneficial in patients with elevated intracerebral hypertension
  - ✓Adverse effects: Hypoxia, propofol infusion syndrome (PRIS), hypertriglyceridemia, injection site reactions, myoclonus, QTc prolongation, hypotension and lowering of intracerebral pressure
  - ✓Contraindications: Hypersensitivity to soy/egg, myocardial depression
- Availability
  - ✓200 mg/20mL, [Infusions; 500 mg/50mL (infusion), 1000 mg/100mL]
- Storage
  - ✓Store at room temperature: 20°C to 25ºC (68°F to 77ºF)

Source: Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Learning Objective Question 1

- Which of the following medication(s) are a controlled substances?
  A. Ketamine
  B. Succinylcholine
  C. Propofol
  D. Etomidate

Learning Objective Answer 1

- Which of the following medication(s) are a controlled substances?
  - **A. Ketamine**
  - B. Succinylcholine
  - C. Propofol
  - D. Etomidate

  Rationale: Ketamine is a Schedule III CDS

Paralysis

- Purpose: To paralyze the skeletal muscles to enhance intubation conditions

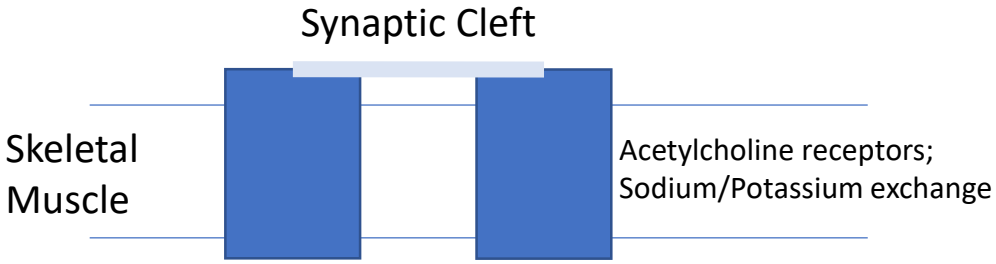
- NMBAs should always be given with a sedative and patients should never be paralyzed while awake; patients should be intubated or in the process of being intubated

- Depolarizing: Succinylcholine
  - ✓Mimics acetylcholine at neuromuscular junctions leading to continuous depolarization to prevent muscle contractions

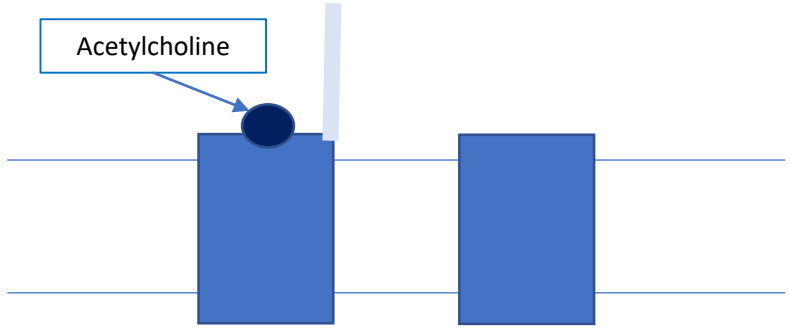
- Non-depolarizing: Rocuronium, Cisatracurium, Vecuronium
  - ✓Competitively inhibits the receptors in the neuromuscular junctions, preventing acetylcholine binding to prevent muscle contractions

Sources: Hampton JP. Am J Health System Pharm. 2011.
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

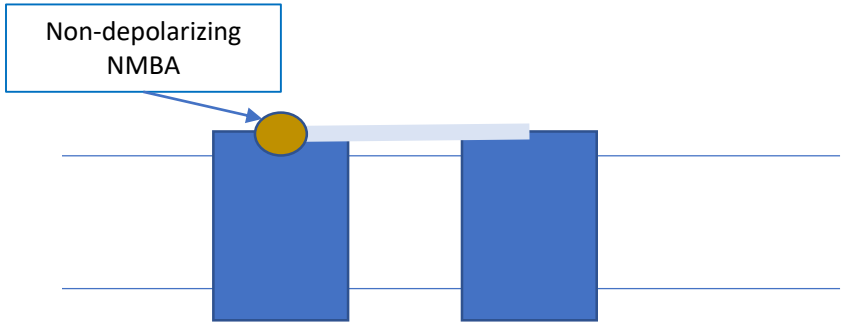
NMBA Pharmacology



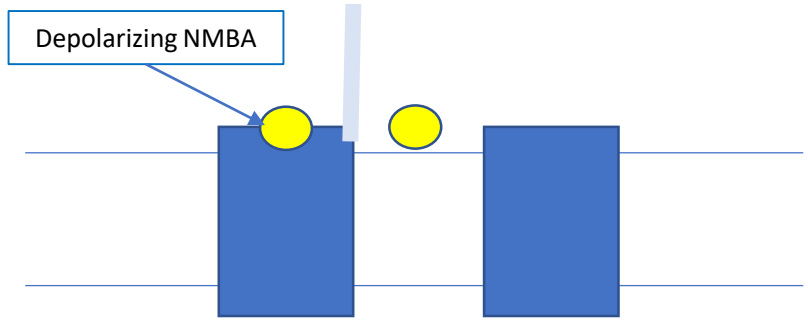
In skeletal muscle during homeostasis the receptor is closed (grey bar).



In skeletal muscle, when stimulated by an agonist (blue circle) the receptor is opened (grey bar).



When the non-depolarizing NMBA (brown circle) binds to the receptor, it closes the receptor (grey bar) and blocks action potential. This is a competitive agonists prevent generation of action potential.



When the depolarizing NMBA (yellow circle) binds to the receptor, it opens the receptor and keeps it open (grey bar). This is an agonists stimulates and maintains the action potential.

NMBA and Body Weight

- NMBA are highly hydrophilic compounds and have a low volume of distribution especially into adipose tissue

- Literature available primarily results from bariatric procedures and small studies; most results demonstrate use of actual body weight results in longer times to recovery

- Underdosing vs Overdosing
  - ✓Overdose usually indicates longer effects of NMBA agent
  - ✓Underdosing may result in failure at first pass intubation

- Patients with extreme obesity (body mass index over 50 kg/m^2)
  - ✓Depolarizing agents: Consider use of actual body weight
  - ✓Non-depolarizing agents: Consider use of adjusted body weight or ideal body weight

Sources: Bhat R, et al. *Am J Emg Med*. 2016.
Murray MJ, et al. *Critical Care Medicine*. 2016.
Thorell A, et al. *World Journal of Surgery.* 2016.
Rocuronium [Package Insert]. Hospira 2019.
Erstad BL, et al. *Anesthesia and Intensive Care*. 2021.
Nightingale CE, et al. *Anesthesia*. 2015.
Succinylcholine [Package Insert]. Hospira. 2019.
Vecuronium [Package Insert]. Bedford Laboratories. 2018.

NMBAs and Pharmacokinetic Overview

Drug	Mechanism	Dosing	Onset/Duration	Elimination
Succinylcholine	Depolarizing	1.5 mg/kg IVP Obesity: Actual Body Weight	Onset: 15-30 seconds Duration: 5-15 minutes	Plasma cholinesterase
Rocuronium	Non-depolarizing	0.6mg-1.2 mg/kg IVP (1mg/kg) Obesity: Ideal Body Weight	Onset: 45-60 seconds Duration: 45-70 minutes	Hepatic, no active metabolites
Vecuronium	Non-depolarizing	0.1 mg/kg IVP Obesity: Ideal Body Weight	Onset: 2-5 minutes Duration: 45-90 minutes	Hepatic via hydrolysis, metabolites eliminated renally
Cisatracurium	Non-depolarizing	0.1-0.2 mg/kg IVP Obesity: Ideal Body Weight	Onset: 45-90 seconds Duration: 45-90 minutes	Hoffman elimination

Sources: Hampton JP. Am J Health System Pharm. 2011.
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Depolarizing NMBA: Succinylcholine

- Dosing RSI: 1-1.5 mg/kg IVP; 4 mg/kg IM (max 150mg)

- Considerations and adverse effects
  - ➢Contraindications: malignant hyperthermia, hyperkalemia, bradycardia, fasciculations
  - ➢Caution in patients with muscle disorders (myasthenia gravis), burns, spinal cord injuries, or crush injuries
  - ➢Adverse effects: Apnea and respiratory depression, hypotension, sinus tachycardia, increase in intraocular pressure, salivation

- Availability
  - ✓2 mg/ mL (10mL) solution

- Storage
  - ✓Store in refrigerator temperature: 2°C to 8ºC (36°F to 46ºF), may be kept at room temperature (20°C to 25ºC) for up to 14 days without significant loss of potency

Sources: Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.
Succinylcholine [Package Insert]. Hospira. 2019.

Non-Depolarizing NMBA: Rocuronium

- Dosing RSI: 0.6-1.2 mg/kg IVP

- Considerations and adverse effects
  - ➢Contraindications: None
  - ➢Caution: Patients with muscle disorders (myasthenia gravis) consider dose reductions; long lasting paralytic ensure post-intubation management
  - ➢Adverse effects: Increase in peripheral vascular resistance (24%), tachycardia, apnea and respiratory depression, hypotension

- Availability
  - ✓5 mg/ mL (5mL or 10mL) solution

- Storage
  - ✓Store in refrigerator temperature: 2°C to 8ºC (36°F to 46ºF), may be kept at room temperature (25ºC) for up to 60 days without significant loss of potency

Sources: Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.
Rocuronium [Package Insert]. Hospira 2019.

Non-Depolarizing NMBA: Vecuronium

- Dosing RSI: 0.08 to 0.1 mg/kg IVP

- Considerations and adverse effects
  - ➢Contraindications: None
  - ➢Caution: Patients with muscle disorders (myasthenia gravis) consider dose reductions; long lasting paralytic ensure post-intubation management; hepatically eliminated
  - ➢Adverse effects: Bradycardia, apnea and respiratory depression, edema, pruritis, skin rash

- Availability
  - ✓10 or 20 mg vial for reconstitution
  - ✓Use 0.9% sodium chloride, dextrose 5%, sterile water for injection

- Storage
  - ✓Store at room temperature: 20°C to 25ºC (68°F to 77ºF)

Sources: Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.
Vecuronium [Package Insert]. Bedford Laboratories. 2018.

Succinylcholine versus Rocuronium

	Paralytic Use	First pass intubation Rate	Sedative Agent Use	Adverse Events	Results
April, MD et al. 2018 Multicenter Retrospective Emergency Airway Registry n=5244	Succinylcholine Mean dose 1.8 mg/kg N=2275	87.0%	Etomidate 84.7% Ketamine 8.4%	14.8%	No association with paralytic choice and rates of first pass intubation success. No association between incidence of peri-intubation events.
	Rocuronium Mean dose 1.2 mg/kg N=1800	87.5%	Etomidate 79.0% Ketamine 14.8%	14.7%	
Guihard B et al. 2019 Noninferiority Multicenter Out of hospital N=1248	Succinylcholine 1mg/kg N=624	79.4%	Etomidate 88.1% Ketamine 5.5%	23.2%	Did not meet non-inferiority, first pass intubation success (difference -4.8, 1-sided 97.5% CI, -9%-infinity).
	Rocuronium 1.2 mg/kg N=624	74.6%	Etomidate 87.9% Ketamine 6.2%	18.2%	

Sources: April MD et al. *Annals of Emergency Medicine* 2018.
Guihard B et al. *JAMA. 2019.*

Learning Objective Question 2

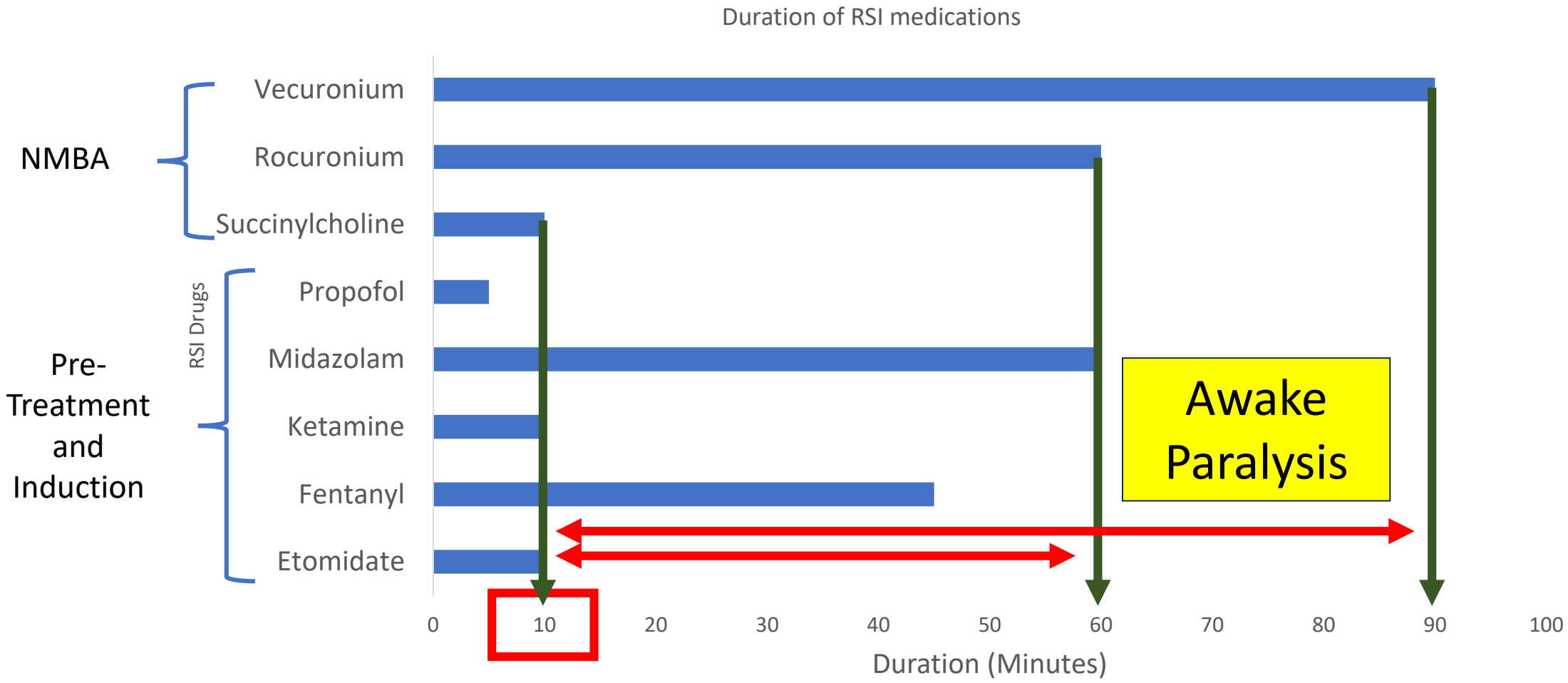
- Which of the following medications are used for rapid sequence intubation?
  A. Naloxone 0.4mg IVP
  B. Succinylcholine 1.5 mg/kg IVP
  C. Ketamine 100 mcg/kg IVP
  D. Calcium Chloride 1000 mg IVP

Learning Objective Answer 2

- Which of the following medications are used for rapid sequence intubation?
  A. Naloxone 0.4mg IVP
  B. Succinylcholine 1.5 mg/kg IVP
  C. Ketamine 100 mcg/kg IVP
  D. Calcium Chloride 1000 mg IVP

Rationale: A. Not indicated in RSI, C. Incorrect dose, D. Not indicated in RSI

Importance of Timely Post-Intubation Management



Sources: Hampton JP. Am J Health System Pharm. 2011.
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Awake Paralysis

- NMBAs are used to block movements of patients primarily in intubations and in the facilitation of mechanical ventilation of critically ill patients
  - ✓These drugs block the ability of a patient to move voluntarily or involuntarily
  - ✓These drugs provide no analgesia and no sedation

- Awake paralysis is when a patient is awake but does not show signs of movement
  - ✓Leads to panic, anxiety, and post-traumatic stress disorder (PTSD)
  - ✓Vitals may demonstrate awareness (e.g. increase in heart rate, blood pressure, end tidal carbon dioxide ($ETCO_2$)
  - ✓Crying or tears

Sources: Hampton JP. Am J Health System Pharm. 2011.
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Neuromuscular blockers

- ED AWARENESS 2021

AIRWAY/ORIGINAL RESEARCH

The ED-AWARENESS Study: A Prospective, Observational Cohort Study of Awareness With Paralysis in Mechanically Ventilated Patients Admitted From the Emergency Department

Ryan D. Pappal, BS, NRP; Brian W. Roberts, MD, MSc; Nicholas M. Mohr, MD, MS; Enyo Ablordeppey, MD, MPH; Brian T. Wessman, MD; Anne M. Drewry, MD; Winston Winkler, BS; Yan Yan, PhD; Marin H. Kollef, MD; Michael S. Avidan, MBBCh; Brian M. Fuller, MD, MSCI*

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✓"I was in the [ED] and I had a mask blowing air into my mouth to help me breathe. I remember the doctors telling me that I would need to be put on the breathing machine. When I woke up, I was lying flat and I could hear everybody's voices around me. I tried to move and breathe but could not and it was terrifying. I heard people in the room talking and I remember seeing the curtains and the lights in the room. I don't know how long this lasted but it **felt like forever**. Then I went to sleep again and the next thing I remember was waking up in the room in the ICU."

✓Reported that he tried to move but could not. He remembers hearing alarms, hearing and seeing 3–4 people standing around his bed and 1 person pulling hard on his injured leg.

✓Said her worst memory was waking up and not being able to move and feeling the pain of endotracheal tube being suctioned.

Source: Pappal RD, et al. *Annals Emergency Medicine*. 2021.

Learning Objective Question 3

- Which of the following is **not** a reason to have timely access for medications for post-intubation management?
  A. To increase the patient's ability to breathe
  B. Prevention of awake paralysis
  C. Minimizes pain as the etiology of agitation
  D. Reduces the sedative agent requirements
  E. Potentially shortens time to extubation

Learning Objective Answer 3

- Which of the following is **not** a reason to have timely access for medications for post-intubation management?
  - **A. To increase the patient's ability to breathe**
  - B. Prevention of awake paralysis
  - C. Minimizes pain as the etiology of agitation
  - D. Reduces the sedative agent requirements
  - E. Potentially shortens time to extubation

Rationale: If the patient is intubated at that point in time, respiratory function is not the primary concern, these agents are to help with answers B, C, D, and E. Having fast access to these post-intubation medications are crucial for all other answers.

Learning Objective Question 4

- Which of the following statements is true, regarding the reason for needing post-intubation medications?
  A. The patient does not need post intubation management, use of paralytics is appropriate
  B. The effects of the induction agents is sufficient for post intubation management
  C. Patients may experience awake paralysis and should have post-intubation medications initiated immediately after RSI
  D. Boluses pain medications should be done after one hour to provide anxiolysis to the patient

Learning Objective Answer 4

- Which of the following statements is true, regarding the reason for needing post-intubation medications?
  - A. The patient does not need post intubation management, use of paralytics is appropriate
  - B. The effects of the induction agents is sufficient for post intubation management
  - **C. Patients may experience awake paralysis and should have post-intubation medications initiated immediately after RSI**
  - D. Boluses pain medications should be done after one hour to provide anxiolysis to the patient

Rationale: Patients should be given post intubation medications (analgesics and sedatives) immediately after RSI as the induction agents wear off sooner than the paralytics (especially with the non-depolarizing agents). Patients should never be paralyzed with a positive RASS score as they may experience awake paralysis.

Analgesia

Atlantic Health System

Post-Intubation Management: Analgesia

- The SCCM guidelines recommend an analgesia-based as first line therapy to keeping mechanically ventilated patients calm and comfortable after intubation
  - ✓Minimizes pain as the etiology of agitation
  - ✓Reduces the sedative agent requirements
  - ✓Potentially shortens time to extubation
  - ✓Not providing pain management can have detrimental effects for patients
    - ➢Short term: increase stress, hypercatabolic state, immune suppression
    - ➢Long term: PTSD, impaired healing, lower quality of life

- Analgesia management
  - ✓Opioids (e.g. fentanyl, hydromorphone)
  - ✓Non-opioid (e.g. acetaminophen, non-steroidal anti-inflammatory, local anesthetics)
  - ✓Non-pharmacologic therapies

Source: Devlin, JW et al. *Crit Care Med*. 2018.

Analgesia: Opioid Continuous Infusions

- IV opioids are 1st line treatment in critically ill mechanically ventilated patients
  - ✓Fentanyl, Hydromorphone, Morphine, Methadone, Remifentanil
- Mechanism: Inhibit the transmission of pain signaling or alter pain perception in the brain, the periphery, and the spinal cord by acting on the mu, kappa, or delta opioid receptors found on neuronal cells
  - ✓Mu receptors: analgesia, euphoria, dependence
  - ✓Kappa receptors: dysphoria, sedation, hallucinations
  - ✓Delta receptors: decreased gastrointestinal (GI) motility
- Adverse effects: Respiratory depression, histamine release, constipation, dependence
- Dosing: Boluses with subsequent infusions based on objective assessment tools for patients unable to communicate with caretakers, follow institutional protocols (e.g. critical care pain observation tool)
- Choice of opioid depends on patient specific factors and drug specific factors
- Storage
  - ✓Controlled substances, refer to specific state regulations and manufacturer recommendations for specific storage locations

Sources: Wang S et al. *Cell Transplantation* 2019. McDonald J et al. *Anesthesia and Intensive Care Medicine* 2005.
Pasternak GW et al. *Neuropharmacology* 2014. Smith HS et al. *J Pain Res.* 2014.
Devlin, JW et al. *Crit Care Med*. 2018.
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Opioids: Therapeutic Effects

	Analgesia	Sedation	Antitussive	Constipation	Respiratory Depression	Emesis	Physical Dependence	MOP activity
Codeine	+	+	+	+	+	+	+	+
Fentanyl	**+++**	**+++**	**+**	**++**	**+++**	**+**	**+++**	**+++**
Hydrocodone	+	+	+++	+			+	**+++**
Hydromorphone	**++**	**+**	**+**	**++**	**+**	**+**	**++**	**+++**
Methadone	++	+	++	++	++	+	+	**+++**
Morphine	**++**	**++**	**+++**	**++**	**++**	**++**	**++**	**+++**
Oxycodone	++	++	+++	++	++	++	++	++
Oxymorphone	++		+	++	+++	+++	+++	++
Tramadol	+	+		++	+	+	+	+

+ Mild effects, ++ Moderate effects, +++ Major effects

Sources: Wang S et al. *Cell Transplantation* 2019. McDonald J et al. *Anesthesia and Intensive Care Medicine* 2005.
Pasternak GW et al. *Neuropharmacology* 2014. Smith HS et al. *J Pain Res.* 2014.
Devlin, JW et al. *Crit Care Med*. 2018.
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Opioids Infusions: Pharmacokinetics and Therapeutic Effects

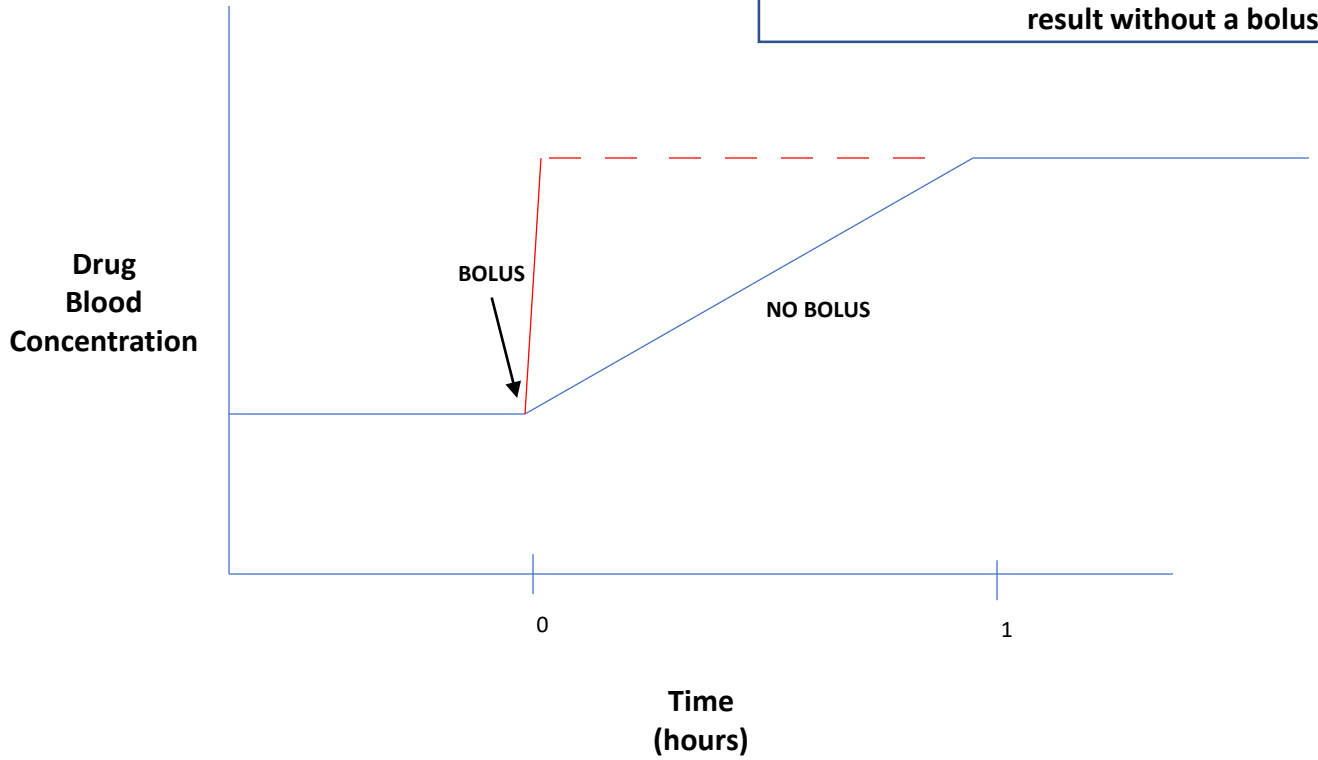
Medication	Onset	Half Life	Side Effects	Other Characteristics
Fentanyl	IVP: 1-2 mins	2-4 hr	Decreased GI motility, chest wall rigidity, bradycardia, hypotension (less than morphine)	Highly lipophilic and may accumulate in hepatic dysfunction and has serotonergic effect
Hydromorphone	IVP: 5-15 mins	2-3 hr	Decreased GI motility, bradycardia, hypotension	Less lipophilic than fentanyl and less affected by hepatic dysfunction than fentanyl
Morphine	IVP: 5-10 mins	3-4 hr	Decreased GI motility, bradycardia, hypotension	Histamine release, accumulates in hepatic and renal impairment
Methadone	PO: 30-60 min IVP: 10-20 min	15-60 hr	Decreased GI motility, bradycardia, hypotension, QTc prolongation, serotonin syndrome	Long-acting agent, may be used to slow tolerance
Oxycodone Immediate Release	PO: 10-15 min	4 hr	Decreased GI motility, nausea, vomiting	May accumulate in renal dysfunction. Can crush tablets or use oral solution.

PO: Oral

Sources: Devlin JW et al. *Crit Care Med*. 2018.
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Pharmacokinetics of Bolus vs. No Bolus

A bolus at the time of infusion rate increase results in almost immediate achievement of higher blood levels and desired effect vs. waiting an hour to achieve the same result without a bolus



Sources: Devlin JW et al. *Crit Care Med*. 2018.
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Sedation

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Post Intubation Management: Sedation Infusions

- After optimization and initiation of analgesia, sedatives are indicated for initiation
- Sedatives are highly lipophilic compounds that cross the blood brain barrier to exert their effects
- Sedatives do not have analgesic properties
- Sedatives are titratable infusions
  - ✓Common titration scales are the Richmond Agitation- Sedation Scale (RASS) or Sedation Analgesia Scale (SAS)
- Titration to a light level of sedation has been shown to have improvement in clinical outcome
  - ✓Light sedation means patient responds to simple commands and is arousable
    - ➢Shorter duration on a ventilator
    - ➢Decrease ICU time/length of stay
    - ➢Decrease incidence of delirium and long-term cognitive dysfunction
    - ➢Decrease dose-dependent side effects
  - ✓Deep sedation means the patient is unresponsive to painful stimuli
    - ➢**Patients receiving paralytics must be in deep sedation**

Sources: Devlin JW et al. *Crit Care Med*. 2018. Finnerup N. *N Engl J Med*. 2019. Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

RASS (Richmond Agitation-Sedation Score)

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior towards staff
+2	Agitated	Frequently non-purposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Sources: Devlin JW et al. *Crit Care Med*. 2018.
Barr J et al. *Crit Care Med* Jan 2013.

Post Intubation Management: Sedatives Infusions

Drug	Mechanism	Onset/Duration	Metabolism and Elimination
Propofol	Non-benzodiazepine with GABA activity	Onset: 1-2 minutes Duration: 3-10 minutes Half life: Short term 3-12 hours, Long term 40-70 hours	Metabolism: Hepatic to water-soluble conjugates Elimination: Renal as metabolites (88%)
Dexmedetomidine	Selective α_2-receptor agonist with sedative	Onset: 5-10 minutes Duration: 60-120 minutes Half life: 2-3 hours	Metabolism: Hepatic through N-glucuronidation and N-methylation Elimination: Renal as metabolites (96%)
Midazolam	Benzodiazepine, binds to GABA	Onset: 2-5 minutes Duration: 2-4 hours Half life: 3-11 hours	Metabolism: Extensive hepatic effects Elimination: Renal as metabolites
Diazepam	Benzodiazepine, binds to GABA	Onset: 2-5 minutes Duration: 30-60 minutes Half life: 3-11 hours	Metabolism: Hepatic through N-demethylation and hydrolysis Elimination: Renal
Lorazepam	Benzodiazepine, binds to GABA	Onset: 5-20 minutes Duration: 6-8 hours Half life: 8-15 hours	Metabolism: Hepatic through conjugation Elimination: Renal as inactive metabolites (88%)

Sources: Devlin JW et al. *Crit Care Med*. 2018. Finnerup N. *N Engl J Med*. 2019. Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Sedation: Propofol continuous infusion

- Sedative effects: Amnesia

- Common adverse effects: Dose-dependent respiratory depression, hypotension, hypertriglyceridemia and acute pancreatitis

- Rare but serious adverse effects: PRIS
  - ✓High doses (> 70 mcg/kg/min) for prolonged use (48 hours)
  - ✓Worsening metabolic acidosis, hypotension with increasing vasopressor needs, arrhythmias, acute kidney injury, hyperkalemia, rhabdomyolysis, and liver dysfunction

- Administration Concerns:
  - ✓Contraindications: Eggs (anaphylaxis) or soy allergy
  - ✓Cloudy appearance, caution with administration for precipitates
  - ✓Do not administer in the same line as blood or plasma; lines should be changed every 12 hours

- Storage and availability: 500 mg/50mL or 1000 mg/100mL (infusion); Store at room temperature: 20°C to 25ºC (68°F to 77ºF)

Sources: Devlin JW et al. *Crit Care Med*. 2018. Finnerup N. *N Engl J Med*. 2019. Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Sedation: Dexmedetomidine (Precedex®) continuous infusion

- Sedative effects: Amnesia

- Considerations and adverse effects
  - ➢ Hypotension (25-50%), bradycardia (5-40%), hypertension (25%), respiratory depression (37%), agitation (5-14%), constipation (6-14%)
  - ➢ Contraindications: None
  - ➢ Caution: Does not achieve deep sedation as monotherapy

- Availability
  - ✓ 200 mg/2mL vials, 200 mg/50mL or 400 mg/100mL (infusion)

- Storage
  - ✓ Store at room temperature: 20°C to 25ºC (68°F to 77ºF)

Sources: Devlin JW et al. *Crit Care Med*. 2018. Finnerup N. *N Engl J Med*. 2019. Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Sedation: Benzodiazepine continuous infusions (Midazolam, Lorazepam, Diazepam)

- Sedative effects: Amnesia, anxiolysis, muscle relaxation, and hypnosis

- Benzodiazepine specific factors
  - ✓Midazolam is the preferred agent based on product stability and pharmacokinetics
  - ✓Potency: Lorazepam > midazolam > diazepam
  - ✓Midazolam and diazepam are more lipid-soluble than lorazepam
    - ➢Quicker onset of action and larger volume of distribution
  - ✓Lorazepam and diazepam contains propylene glycol as a solvent which can lead to toxicity at higher doses
    - ➢Causing hyperosmolar state, anion gap metabolic acidosis, acute kidney injury or multisystem organ failure

- Metabolites accumulate with prolonged administration
  - ✓Geriatrics
  - ✓Renal impairment or hepatic impairment
  - ✓Heart failure

- Storage and availability: Compounded sterile products, refer to institutional practices and guidelines; Controlled substances

Sources: Devlin JW et al. *Crit Care Med*. 2018. Finnerup N. *N Engl J Med*. 2019. Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Learning Objective Question 5

- Which of the following agents are recommended as first line therapy for patients who are receiving sedation and analgesia?
  A. Ketorolac 15mg IVP and midazolam 4mg IVP
  B. Hydromorphone infusion and morphine infusion
  C. Morphine infusion and diazepam infusion
  D. Fentanyl (bolus and infusion) and propofol

Learning Objective Answer 5

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  A. Ketorolac 15mg IVP and midazolam 4mg IVP
  B. Hydromorphone infusion and morphine infusion
  C. Morphine infusion and diazepam infusion
  D. Fentanyl (bolus and infusion) and propofol

Rationale: A. Ketorolac would not provide adequate pain control, opioids are first line. B. Hydromorphone and morphine are both opioids there is no sedative agent. C. Morphine has higher rates of ADR and diazepam is not preferred due to stability concerns.

Neuromuscular Blockade (NMBA) Infusions

- Ensure deep sedation (e.g. RASS score -5) to ensure complete sedation with the use of propofol or benzodiazepines only; other agents will not provide deep sedation

- Confirm weight that is being used in the order (use of actual, adjusted or ideal body weight may vary by institution)

- Confirm the clinical goals
  - ✓Monitoring through train of four or bispectral index (BIS) may not always provide an accurate depiction of sedation state

- Common NMBA choices
  - ✓Cisatracurium is the preferred agent as it has a shorter half-life and is eliminated via Hoffman elimination
  - ✓Vecuronium should be avoided in patients with renal or hepatic insufficiency

Sources: Devlin JW et al. *Crit Care Med*. 2018. Finnerup N. *N Engl J Med*. 2019. Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

NMBA Storage and Safety Recommendations from Institute for Safe Medication Practices (ISMP)

Atlantic Health System

NMBA Best Safety Practices: 2016 ISMP Recommendations for Facility Evaluation

- Administration
  - ✓Indication
    - ➢For patients are **intubated or are in the process of being intubated**
    - ➢Do not administer NMBA medications after extubation, for agitation or punishment
  - ✓Ensure **sufficient sedation** has been administered prior to prevent awake paralysis
  - ✓Use barcode medication scanning
  - ✓**Flush lines completely**
  - ✓Use smart infusion pumps
  - ✓Label all syringes and lines
  - ✓Discard all unused vials or waste immediately
- **Review storage and safety**
  - ✓Look-alike packaging, labeling, and drug names
  - ✓Affix labels with warnings
  - ✓Limit access and segregate storage
  - ✓Provide access to reversal agents
- Use clear terminology (e.g. neuromuscular blocking or paralyzing agents instead of muscle relaxants)
- **Provide education, competency, and awareness**

Sources: Institute for Safe Medical Practices (ISMP). 2016 (https://www.ismp.org/resources/paralyzed-mistakes-reassess-safety-neuromuscular-blockers-your-facility)
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

NMBA Resulting in Patient Death

- National news over a 2017 fatal medication related event involving NMBA
- Patient was scheduled to undergo a PET scan and wanted something to relax
- Medication order was placed for midazolam (Versed®)
- Nurse typed in "**VE**" into the automated dispensing cabinet (ADC), trying to select the brand name of the drug, **VE**rsed
- What she pulled out was vecuronium
- Vecuronium was administered inadvertently
- Patient was paralyzed and stopped breathing in the imaging department, code was called, patient was revived and taken to intensive care but had anoxic brain injury
- The following day patient declined clinically, and patient passed after termination of life support

Sources: Institute for Safe Medical Practices (ISMP). 2019 https://www.ismp.org/resources/safety-enhancements-every-hospital-must-consider-wake-another-tragic-neuromuscular)
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

NMBA and 2019 Institute of Safe Medication Practices (ISMP) Recommendations

Plan for sedation especially for sedation prior procedures causing claustrophobia	Include IV moderate sedation agents on high-alert medication lists	Store neuromuscular blocking agents in appropriate areas	Affix warning labels
Barcode medication scanning	Require patient monitoring	Avoid reconstitution using flush syringes	Monitor overrides, review policies, witness requirements
Adoption of culture of safety	Education	ADC vendor recommendations: Increase number of letters required for searching for medications	Manufacturer/regulatory agencies: Improvements to labeling of NMBA to include statements "WARNING: Paralyzing Agent" in bold red font on the carton and label

Sources: Institute for Safe Medical Practices (ISMP). 2019 https://www.ismp.org/resources/safety-enhancements-every-hospital-must-consider-wake-another-tragic-neuromuscular)
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

NMBA in the ADC: ISMP Recommendations

General Features

- Optimize profiled ADC for drug selection
- Manage override lists
- Block staff from loading inappropriate medications
- Utilize warnings during medication removal
- Witness for override medication removal
- Allow simultaneous searching by brand and generic names
- Support distraction-free ADC medication removal

Neuromuscular Blocker Safety Features

- Limit access: Users, location, locking bins
- Affix warning to ADC pockets

Sources: Institute for Safe Medical Practices (ISMP). 2019 https://www.ismp.org/resources/safety-enhancements-every-hospital-must-consider-wake-another-tragic-neuromuscular)
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/. Updated 2021.

Institutional Experiences

ADC Removal

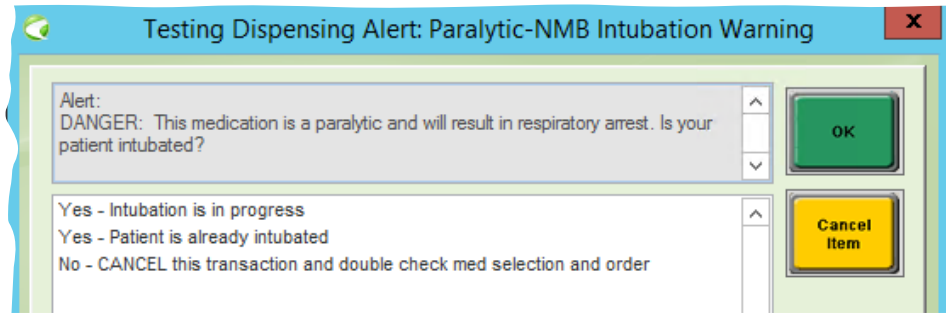
- Override reviews
- Compounded syringes in locked bin
- Vials stored under refrigeration in bright orange bins
- ADC interactive alerts

Administration

- Barcode medication administration
- Dual sign-off with a witness

Storage/Dispensing

- Affixed warning labels
- Limited to emergency department, intensive care areas, operating areas
- Continuous infusions are in locked bins for storage of NMBA
- Delivering via courier only
- Do not send through pneumatic tubes



Learning Objective Question 6

- NMBA should be stored appropriately to mitigate medication errors. Which of the following are some considerations that should **not** be taken?
  A. NMBA should be stored in a locked or segregated area
  B. NMBA should be placed in the ADC and barcode scanning turned off
  C. NMBA, if allowable to be on override, should be reviewed on a regular basis
  D. NMBA storage in the ADC should be limited to certain areas

Learning Objective Answer 6

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  - **B. NMBA should be placed in the ADC and barcode scanning turned off**
  - C. NMBA, if allowable to be on override, should be reviewed on a regular basis
  - D. NMBA storage in the ADC should be limited to certain areas

Rationale: Barcode scanning should NOT be turned off

Summary

- Rapid sequence intubation's role is to make the emergent intubation easier and safer to increase success rates of intubation and decrease complications

- Medications are critical in the steps of Preparation, Pre-treatment, Paralysis with induction, and Post-intubation management steps

- Avoid awake paralysis
  - ✓Induction agents should always be given before paralytics

  - ✓Analgesia and sedation should be initiated immediately after RSI especially if there was use of NMBA
    - ➢Opioids are the first line therapy and can decrease use of agents for light sedation
    - ➢Sedation should be optimized with propofol, dexmedetomidine, or benzodiazepines (midazolam)

- Titration to analgesics and sedatives to appropriate institutional scores
  - ✓Deep sedation (e.g. RASS -5) with propofol or benzodiazepines is required for patient on paralytic infusions (cisatracurium, vecuronium, rocuronium) to prevent awake paralysis

- ISMP has recommendations to evaluate NMBA medication use process to prevent patient harm
  - ✓Evaluate institutional specific practices for improving medication use especially with paralytics
  - ✓Indication and use of paralytics as IV push and continuous infusions should be understood including RSI, prevention of shivering in hypothermia management, or ventilator dyssynchrony

Sources: Hampton JP. *Am J Health System Pharm*. 2011.
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