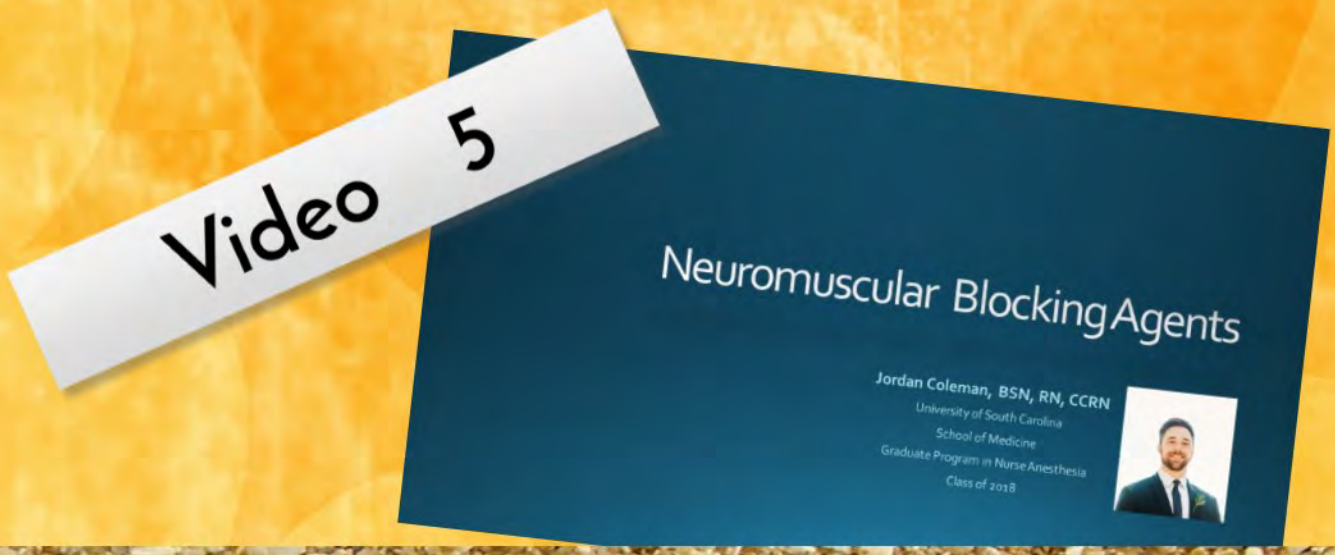
Anesthesia for Post Anesthesia Care Nurses



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STORM ANESTHESIA

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Introduction

Welcome to Storm Anesthesia's Anesthesia for Post Anesthesia Care nurses. This is a seven-video series on the basics on pharmacology and anesthesia techniques for the perianesthesia care nurse.

We, a group of five senior students from the University of South Carolina School of Medicine Nurse Anesthesia Program and one CRNA, have created this series in the hopes it will help the transition into the perianesthesia world. The series attempts to shine a bit of light on the techniques anesthesia uses during surgery, as well as explain the basics of the pharmacology behind our drug uses. This is by no means a series that will explain everything that happens during anesthesia, but our hope is that you, the perianesthesia nurse, will find our report a little less intimidating and a little more informative. After all, the better you understand the report, the better you can take care of the patient, and ultimately, this will increase the safety and satisfaction for both your patients and yourself.

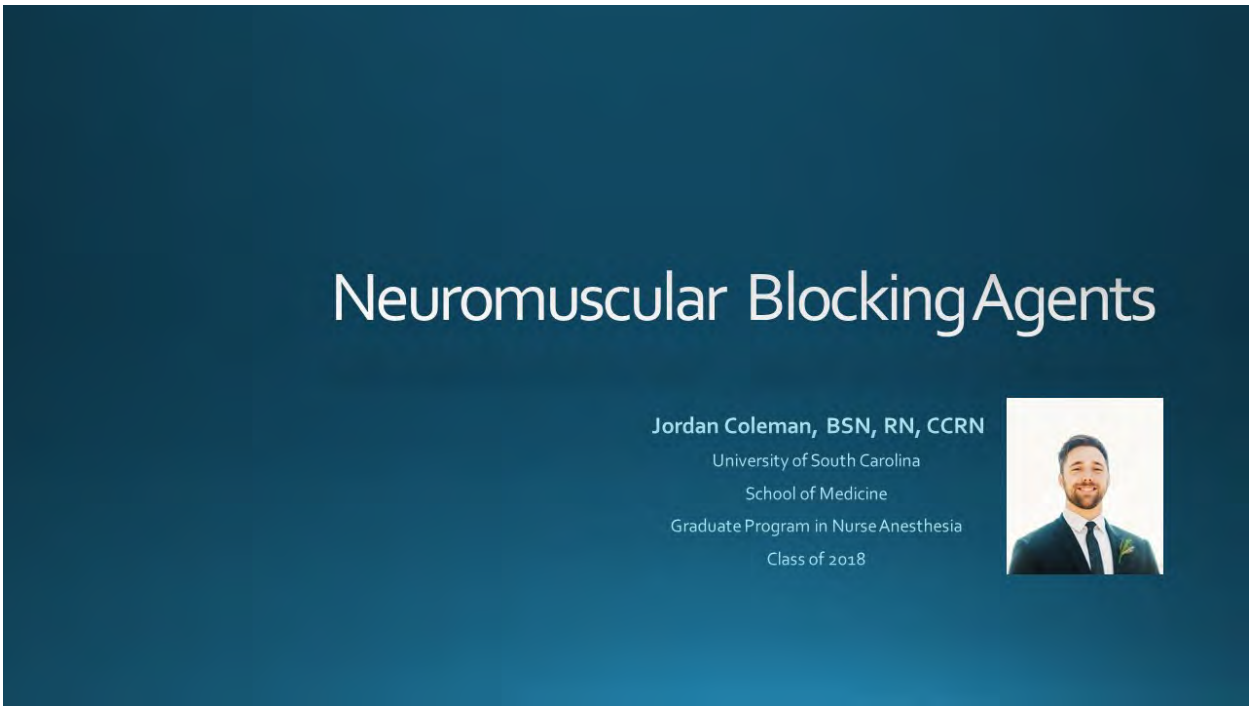
The group consists of Alexandra Harman, BSN, RN; Braiden Sightler, BSN, RN; Jordan Coleman, BSN, RN, CCRN; Kelsey Squires, BSN, RN, CCRN; Victoria Koke, BSN, RN; and Michael Storm, DNAP, CRNA, CCRN.

The videos can be watched separately, but there are some references among the videos and the basics of the pharmacology along the way. Therefore, it may be beneficial to watch the series in order. Either way, have fun and don't forget to download the accompanying handouts. These handouts are the complete transcripts of the narrations and include all relevant pictures from the videos.

This video-series is sponsored by Storm Anesthesia and Palmetto Health Richland Anesthesia Department.

Enjoy and let's get started.

Michael Storm, DNAP, CRNA, CCRN
Editor
November 2017



Neuromuscular Blocking Agents

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Class of 2018

Hello everyone, my name is Jordan Coleman. I am a senior student nurse anesthetist at USC with the class of 2018. I'm very excited to be talking to you about neuromuscular blocking agents. This is a topic that is important to you as these drugs are commonly used during surgery and you are the excellent providers that are recovering the patients we use them on. It will be greatly beneficial to all of you, I think, to be familiar with these drugs and how they work on a deeper level because it will allow you to have a better understanding of what's going on under the surface with some of your patients as they are in the recovery process.

Goals

Our goals for this lecture are to understand the benefits and risks of NMBDs during anesthesia. Become more familiar with the side effects of NMBDs and the reversal agents we use. These first two points are going to make up the bulk of this lecture. If you understand the underlying anatomy and physiology of why and how these drugs work, you are going to be golden. Instead of memorizing a slew of numbers and side effects, this information will sink in and you'll remember as a result. We also want to know how to monitor depth of blockade and adequacy of reversal. And to wrap things up we will look at some other assessment tools that you can use to help provide safer care for our patients.

Overview

Just a quick look at how we will proceed through topics over the next 50 minutes: we will start with a review of nerve conduction as well as the transition of the neuromuscular junction. This is where all our drugs work so we'll spend a good bit of time here.

Next, we'll dig into the specific drugs we use to relax our patients and the differences between them.

After that we are going to spend some time reviewing the anatomy and physiology of the autonomic nervous system. This is so important because our reversal agents, which we will discuss afterwards, have a huge impact on these systems.

We will touch briefly on how we monitor the depth of blockade during anesthesia, as well as physical assessments.

Ultimately, I want you to walk away feeling like you have a better understanding of what's going on beneath the surface with these drugs. I want you to feel like you can provide safer care to your patients and be prepared for complications you may see in the future.

Keywords and Definitions

Here are a few quick keywords I want to sync us up on before we get going.

Fasciculations: Skeletal muscle twitches

Myopathy: An abnormal condition of skeletal muscle characterized by muscle weakness and wasting.

Neurohormonal Transmission: Combined electric and chemical transmission of an impulse.

Nicotinic: Subset of parasympathetic nervous system

Onset time: The time it takes a NMBD to reach maximum effect after administration.

Pseudocholinesterase: An enzyme that acts like cholinesterase and metabolizes acetylcholine.

Recovery Index: In reference to the use of NMBDs, the time it takes a train-of-four twitch index of 25% to 75% recovery of the twitch response.

Train-of-Four Ratio: A comparison made between the fourth and first twitch in the train-of-four test; when the fourth twitch is 90% of the first twitch, full recovery is indicated.

Neurotransmitter: Chemical produced by nerve cells to send signals to other cells

Acetylcholine (Ach): A specific neurotransmitter

Action Potential (AP): A brief reversal of transmembrane voltage across an excitable membrane.

Polarization: A difference in electrical charge in one part of a cell compared to another part of the same cell.

Neuromuscular Junction (NMJ): The point at which a neuron connects to a muscle fiber.

Competitive Antagonist: A substance that binds to a receptor but does not activate it. Must compete with other substances to bind.

Anticholinesterase: A drug that inhibits the action of acetylcholinesterase.

Antimuscarinic: A drug that blocks the effects of the acetylcholine receptors and results in the transmission inhibition of the parasympathetic nerve impulses.

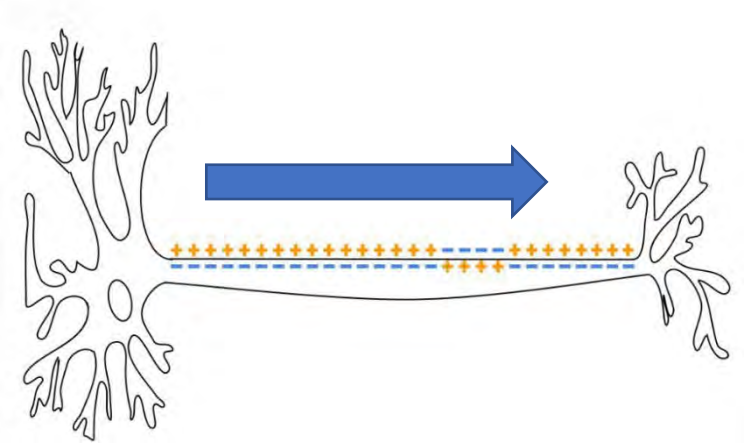
Clinical Duration: The after administration to 25% recovery of the train-of-four response.

Defasciculation: Giving a subclinical dose of a non-depolarizing agent prior to a depolarizing agent to prevent muscle twitches and subsequent myalgias.

Most of these I'll explain multiple times but if you want to reference any of them, feel free to return here at any point.

Action Potential

Let's start with a quick refresher on nerve cell conduction because it's important to understand how NMBDs work.



On the left of this picture is the cell body, the long stalk in the middle is the axon, and on right are the axon terminals. Cell signaling moves left to right. As you'll notice there are some plus signs outside of the axon and negative signs inside. This is because, at a resting state, neurons have a negative charge relative to the outside of the cell. This is also known as being polarized; each side has a different charge. This is a result of electrolyte concentrations. Outside of the cell is large concentration of sodium, while the inside contains a lot of potassium. These concentrations are maintained with the sodium-potassium-pump. An easy to way remember which one is on which side is this: look at the serum values for these two, Na is 135-145 while potassium is only about 3.5-5. Why is potassium so much lower? Because it's all inside the cells, and therefore not floating around freely in the blood like sodium is.

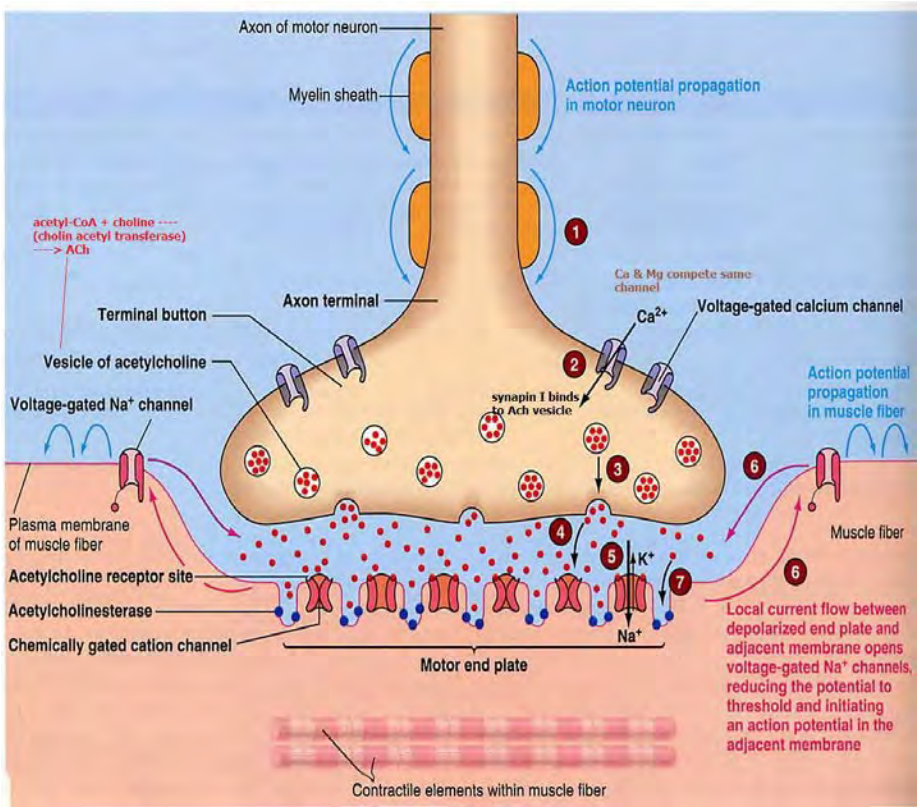
So how does the nerve signal other cells? Well, all along this axon there are a lot of Na and K channels. At rest, these channels are closed. For the channels to open, they must be signaled by an electrical impulse. When the cell body is signaled by another cell it will funnel an electrical impulse down into the axon. At this point, the sodium channels begin to open. As sodium floods into the cell, it's going to make the inside become more positive, until eventually, a threshold is achieved. This is called depolarization, the loss of the resting electrical charge. As depolarization occurs, the sodium channels adjacent to them also open, which is what allows the signal to be carried down the length of the nerve. As this happens, potassium channels open, causing potassium to exit the cell. This is what causes repolarization; a reset of the. charge of the cell at rest.

An Action potential is an all-or none phenomenon, meaning it either happens or it doesn't. If a cell doesn't reach threshold, it won't fire, and if it does reach threshold, it fires completely. There is no partial action potential.

As the signal reaches the axon terminals, the mechanism for continuing the signal to muscle fibers, is going to change slightly. Which brings us to….

Anatomy of the Neuromuscular Junction (NMJ)

The Neuromuscular Junction is where the nerve meets the muscle fiber. How does the neuron signal to the muscle fiber that it needs to contract? This is a busy picture but just follow along the numbers with me one at a time. To orient you to the picture, the top portion is the axon terminal, and the base of the photo is the muscle fiber, AKA the motor end plate. All the red dots floating around in between and in those little bubbles of the axon terminal are the acetylcholine molecules.



- We've reached the end of our axon as the action potential has travelled down the length of the neuron. We're at the axon terminal.
- As the AP reaches the terminal, it causes calcium channels to open. Think of Ca as the hook that allows these vesicles to attach to the base membrane of the nerve.
- Ach is then dumped into the synaptic cleft, the gap between the terminal and muscle fiber.
- Ach then diffuses across the cleft and…
- Attaches to Ach receptors. These are just Na channels that require acetylcholine to open them, rather than an electrical signal. When two Ach molecules bind to the receptor, the channel will open, and Na will flood in, just like it did along the axon. This is going to cause the same action potential effect in the muscle fiber that it did along the neuron.
- Adjacent Na-channels will send the signal along the length of the muscle fiber. The actual mechanics of muscle contraction are beyond our needs for this lecture, so just remember that Ach receptors opening is required for muscle contraction.
- The last step is what ends the signal. We must be able to end the signal or else our muscles would be contracting all the time. There's an enzyme called Acetylcholinesterase located in the folds of the motor endplate. These are the little blue dots you see around the receptors. These break down Ach very quickly, ending the signal from the neuron. These will come into play later when we talk about reversal of neuromuscular blockade

So, that's our quick refresher on the signaling of muscle contraction. In a few slides we are going to zoom in a little more on the acetylcholine receptors to get an even closer look at how our drugs work.

How NMBDs work

So how do our drugs work to block this process?

The drugs we use are called competitive antagonists. You may remember from your pharmacokinetics lecture that these drugs must compete with other substances to bind to their desired receptors. And antagonists will bind to a receptor, but not activate it. As such, our paralytic agents will lock onto an Ach receptor without activating it, and simultaneously prevent acetylcholine from binding and activate it. This leaves our muscles unable to contract since the AP cannot traverse the synaptic cleft. If the Ach receptors don't activate, there is no muscle contraction.

Simple concept, right? You can't call a friend on your cell phone if the satellite that relays the signal is broken, even if both phones are working fine. It's a similar idea for our muscles. Without the signal, there is no contraction.

Why do we use them?

Our first purpose for NMBDs, as anesthesia providers, is to facilitate intubation. The jaw and airway muscles are tight and make it difficult to intubate without relaxing them first.

Also, some surgeries require muscle relaxation: Many abdominal surgeries (especially laparoscopic), Total joint replacements, spinal surgeries, open heart, thoracotomies, robotic surgeries, and others.

They facilitate the work of the surgeon by reducing muscle tension when opening and closing the incision, or when anatomy manipulation is required, such as with joint replacements.

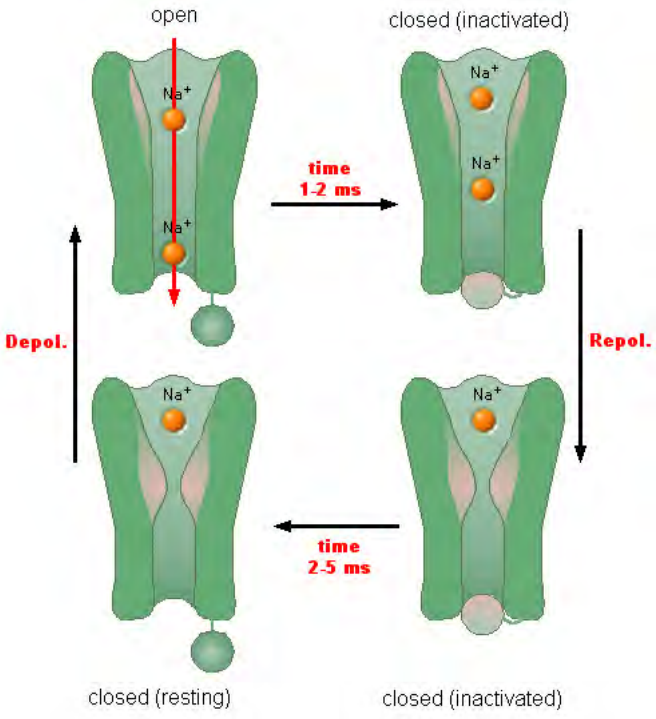
And last, but not least, patient safety is maintained with these drugs. Some surgeries are performed on very sensitive anatomy, (like the heart or lungs). Even though patients are anesthetized with IV drugs and inhalation agents, they can still have reflexive movement, such as coughing. The patient isn't necessarily aware when this happens because they are anesthetized, but we like to prevent coughing in situations when even small movements can cause inadvertent lacerations with surgical tools.

So, we're not just using them without reason, they serve a very important purpose.

Types of Neuromuscular Blocking Drugs (NMBDs)

Let's look at the types of NMBDs. There are only two classes: depolarizing, and non-depolarizing.

- The Depolarizing drugs bind to the Ach receptor, activate it, but then stay attached to the receptor, preventing it from reactivating.
- The Non-depolarizing drugs simply bind to the Ach receptor and prevent it from opening.



To make a little more sense of this idea, let's look at this picture. This is the progression of opening and closing for the Ach receptor. The bottom left is our resting state. The channel is closed, and Na cannot pass through. When Ach binds to the receptor (here and here), the channel opens, and yes it does take two Ach molecules to activate a channel.

This moves us straight up where the channel is opened, allowing Na to travel through. But the channel only stays open briefly, approximately 1-2 milliseconds.

This moves us to the top right picture. Notice here as well that there is a little green circle at the base of the receptor. Think of this as a safety latch. After a channel is opened briefly, this latch will close, effectively blocking further diffusion of Na. This is the inactivate state. Even though the channel is physically open, the latch has inactivated it. The receptor cannot fire again from this state, it must be reactivated by repolarizing. This happens when Ach detaches from the receptor, allowing for repolarization to take place, which takes about 2-5 milliseconds. So, this is a very fast process.

A decent analogy for this is a gun with one bullet. You've got a gun that is cocked and loaded. This is the resting state. When you pull the trigger, the bullet fires. This is the open state. At this point, though, the ammunition has been expended so the gun is unable to fire again as it is. It must be reloaded and cocked again, which will bring it back to it its resting state.

So back to our drugs,

The depolarizing drugs work by attaching to the receptor and activating it, but the drug will remain on the receptor after activation. This leaves it in its inactivated state until the drug is taken away.

Non-depolarizing drugs work by simply binding to the receptor in its resting state, and leaving it here until it's removed from the receptor.

The Depolarizing Neuromuscular Blocking Drugs

So, we're finally getting to look at some of our drugs! We're going to start with our depolarizing NMBDs, which should be simple, since there is only one.

Succinylcholine (Anectine)

Succinylcholine is the only depolarizing NMBD we use in anesthesia. It's a very fast acting agent, it's fast on and fast off. Time of onset is about 60 seconds. And it lasts about 4-5 minutes until the patient can begin breathing again, with complete reversal in 10-12 minutes. It's main use nowadays is to facilitate endotracheal intubation during anesthesia induction. This is because of its short duration, which proves to be especially beneficial if the surgery does not require muscle relaxation by the surgeon. It is also the drug of choice for Rapid Sequence Induction (RSI). This is when we give propofol and succinylcholine simultaneously and hold pressure on the cricoid cartilage, which is done to occlude the esophagus. This is done in situations when intubation needs to be done for the safety of the patient but their NPO status is inadequate or unknown, such as in trauma patients, or emergency C-sections. The goal of RSI is to prevent vomiting and aspiration in high risk patients, so we like drugs that work quickly.

Succinylcholine is also metabolized differently than our other NMBDs. There is an enzyme called pseudocholinesterase that is very similar to acetylcholinesterase but does not break down acetylcholine. This enzyme's activity is the reason the drug only lasts a short while. It's important to note that a small number of people do have genetic variances that effect the pseudocholinesterase enzymes ability. In these patients, the enzyme is much slower, resulting in prolonged paralysis for anywhere between 1-6 hours. These patients will require postop ventilation until the drugs wears off. And because it is so rare, we don't test people for it prior to surgery but if we do find that someone has a very prolonged effect from succinylcholine, then we would make sure to note it on his or her chart and avoid it in the future. They would also need to undergo genetic testing and most likely his or her family members would need testing, as this characteristic can be shared amongst relatives.

Adverse effects of succinylcholine

You'll see in this slide that succinylcholine has some potentially significant side effects. A lot of these have to do with its depolarizing effect. Remember that because it is initially causing that depolarization of the muscle fibers, that those fibers are going to contract. And since we can't just direct our drugs to one area of the body, this causes all the skeletal muscles of the entire body to contract before relaxing. We call these contractions fasciculations. All the muscles spastically contract for about 10-15 seconds at about the 30 second mark after administration. Sometimes in patients with significant muscle mass, this can be a big display with arms coming off the table, but in most it looks like twitching of the whole body for a few seconds. However, this can cause fairly significant muscle pain, or myalgias, over the following days. It's the same concept as working out really hard after not working out for a long time. That intense feeling of soreness you get the next couple of days is the exact same soreness some people feel the

following days after getting this drug. Not everyone has it, but plenty do. Some anesthesia providers will treat this by giving a very small dose of a non-depolarizing drug just prior to giving the succinylcholine, which prevents the fasciculations from occurring. However, not everyone utilizes this technique.

Next is an increase in potassium. Remember how potassium is inside the cells at rest. Well if we contract every skeletal muscle in the body at once, that's a decent amount of potassium exiting the cell and entering the extracellular fluid at one time, and some of that will enter the vasculature, which is why we see this rise in potassium. This is a transient effect however, which returns to baseline in about 10-15 minutes. But checking electrolyte levels before giving this drug is very important, especially if a patient has kidney disease, because they often have higher potassium levels to begin with and the increase in potassium is less predictable. Use of succinylcholine is contraindicated if K>5.5mEq/L, but many people will avoid it if K>5mEq/L.

The next 4 side effects are a result of succinylcholine's similar structure to acetylcholine. It can activate some other cholinergic receptors in the body. We'll consider where these receptors are in a little bit when we look at our reversal drugs but for now, just know that it can cause bradycardia in children, increased ICP, increased IOP, and increased intragastric pressure. For the bradycardia in children, we avoid succinylcholine except in emergencies and when we do give it, we also give some atropine to counter the bradycardia it can cause. In patients with increased or suspected increased ICP, we would avoid it. In patients with glaucoma, we'd avoid it. Intragastric pressure is not something we normally measure, and this rarely causes any noticeable symptoms, but it's worth noting that in can occur.

We talked about the prolonged blockade in genetically predisposed patients. Leaving us Malignant Hyperthermia or MH. You probably remember hearing of this in your lecture on the volatile anesthetic agents. Succinylcholine is the only other anesthetic drug we currently use that can cause MH. I won't spend much time on it for that reason, but just remember that it can cause elevated temperature, tachycardia, significant muscle rigidity, acidosis, and irregular respirations. And it is treated with Dantrolene. We don't know the exact mechanism for why it causes MH, but only that it does.

Now if you're thinking to yourself, wow, this drug sound pretty harmful. The reality is that the serious side effects of this drug are usually avoided by not giving it to those who are high risk, as we talked about. And the prolonged blockade and MH it causes are extremely rare. And the truth is that it just works well. It does the job it is needed for very well. Some people still avoid it because of the side effects but many people will continue to use it until something else comes along to replace it.

The Non-Depolarizing Neuromuscular Blocking Drugs

Now we are going to switch gears and talk about the non-depolarizing NMBDs. As the name implies these drugs do not cause depolarization at the NMJ like succinylcholine does. Let's see how these drugs work.

Curare Plant

Here is a little background information for you about where our non-depolarizers came from. This is the curare plants AKA Chondrodendron Tomentosum. It is a vine found in South America that was originally used as a poison by indigenous tribes. They would crush it up and dip their arrows into it before hunting to aid in killing their prey. We know now the mechanism of how this plant works. It causes paralysis, specifically of the diaphragm, and as a result the animals would suffocate and die. Pretty harsh, but effective. It was not until the 1930s that scientists began to apply the effects of the plant to drugs that could be used for anesthesia and surgery. But since then there has been a lot of research and development and there will continue to be well into the future.

Classes of ND-NMBDs

Class	Drug	Dose (mg/kg)	Time of Onset	Elimination Half-life (min)	Duration of Action (min)
Short Acting	Mivacurium		3-4	2.4	15-20
Intermediate-Acting	Rocuronium	0.6 - 1.2	1-3	80	30-90
	Vecuronium	0.05 - 0.1	3-4	70	35-45
	Atracurium	0.25 - 0.5	3-4	20	35-45
	Cisatracurium	0.05 - 0.1	5-7	23	35-45
Long-Acting	Doxacurium		5-10	95	40-120
	d-tubocurarine		2-4	90	60-120
	Pancuronium		2-4	140	60-120

This is a list of several non-depolarizing NMBDs, and there are others not listed here that are not really seen in practice anymore. You may notice that they all contain the stem –cur in the middle of their names, as a result of being developed from the curare plant we just discussed. But they are categorized based on duration of action: short, intermediate, and long acting. I've highlighted the intermediate-acting class because these are really the only drugs you'll see being used currently, and even then, a couple of them are still infrequently seen. Rocuronium is the most common drug we use, for reasons we will come to shortly. Followed by vecuronium.

Atracurium and cisatracurium are not used as frequently but are typically reserved for special considerations. But they all have very similar durations of action. However, duration is very dose dependent, so these numbers are just averages.

Let's look at the time of onset in this table. You'll see that rocuronium has the fastest onset of the four. When given in higher doses, it can get down to about the same time of onset as succinylcholine, about 45-90 seconds. Why don't we use rocuronium to intubate everyone with then? Well, when we give it at doses high enough to achieve this quick onset, it lasts a much longer time. Up to 90 minutes. The 30-40-minute duration we see in this table is more related to intraoperative dosing, which is typically less than an intubating dose. The other drugs take a few minutes to achieve the desired level of relaxation and so are not used for intubation unless rocuronium is unavailable, which has been the case recently due to some issues with the manufacturer. However, that seems to have resolved at this point.

You may also notice that the elimination half-life does not seem to match up with the duration of action. This is a result of redistribution. You may remember this concept from your pharmacokinetics and pharmacodynamics lecture. This is the idea that a drug that moves away from the receptors back into the vasculature cannot exert their effects on the receptor. And since the only part of the drug that is metabolized is the drug in the vasculature, that means that the drug at the receptors are not being metabolized until they redistribute back into the blood circulation. So, as a result, the half-life is different from the duration of action.

Rocuronium & Vecuronium

Let's start with rocuronium and vecuronium, which are very similar to each other. They are both aminosteroid compounds. Vecuronium is metabolized by the liver and kidneys and does have an active metabolite with 80% of the potency of vecuronium. Rocuronium is excreted unchanged in bile and urine.

We talked in the previous slide about how rocuronium has a much faster onset but can last much longer at those doses. Despite its long duration of action (DoA), it can be used as an alternative to succinylcholine for RSI. If there are obvious contraindications to succinylcholine, rocuronium is the only other option for a true RSI, and we will just have to accept and deal with its duration.

Vecuronium is 6x more potent than rocuronium, which simply means we can give less drug to achieve the same results.

Anaphylaxis has been described with rocuronium, but is extremely rare. And some have even questioned the validity of the diagnosis. Fortunately, these drugs do not have any other major side effects.

These two drugs are the bread and butter of paralytics. 99% of the time, one of these two is the drug that was used to relax your patient during surgery.

Atracurium & Cisatracurium

Now let's talk about atracurium and cisatracurium. These drugs are not aminosteroids, but rather benzylisoquinoline compounds. What makes these two drugs unique is that they are not metabolized by the liver or kidneys. They utilize something called Hoffman degradation, as well as nonspecific plasma esterases.

Hoffman degradation is a process that is influenced by body temperature as well as pH. As temperature and pH increase, so does the rate of metabolism. If temperature and pH go down, metabolism slows down. I've seen this before in a patient that we were struggling to keep warm intraoperative, and towards the end of the surgery, the patient was still deeply paralyzed even though our dosing indicated that it should have worn off by then. Eventually we could reverse it, but we had to wait a bit.

The plasma esterases are just enzymes that float around in our blood. They work on a few other drugs as well such as esmolol and remifentanil. But both processes work together to metabolize these drugs. And as you can imagine, this can be a huge benefit for patients with liver or kidney disease. We don't have to worry about prolonged effects and trying to guess how long rocuronium or vecuronium are going to stick around. We can just use one of these two drugs instead.

A couple of things about atracurium:

1) One of the metabolic byproducts of atracurium is a compound called laudanosine. This compound has been shown to cause seizures in animals, but only in doses higher than we use for anesthesia. However, laudanosine toxicity is still a concern to look out for.
2) Atracurium causes histamine release, especially when we give it at higher doses. This causes hypotension, tachycardia, and skin flushing. Which sounds and looks a lot like anaphylaxis but it's not a true anaphylactic reaction. It is this histamine release that has caused atracurium to fall out of favor by many.

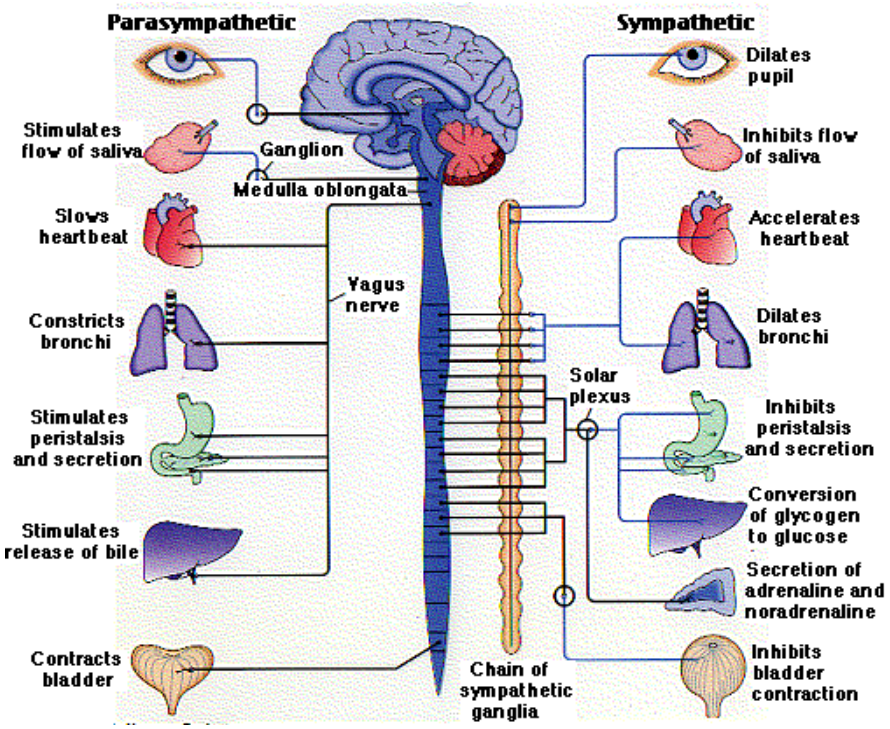
Cisatracurium was developed as a drug that would not have these issues. It's an enantiomer of atracurium, or one of its isomers that was isolated from the other. While cisatracurium can cause histamine release, the doses required to do so are so high that we'd never encounter them clinically, essentially eliminating the histamine release problem. And laudanosine production is significantly smaller as well, thus eliminating this concern clinically. The major disadvantage is that it is expensive. So, a lot of people will still use atracurium for liver and kidney patients before cisatracurium. Although if a drip were to be used, cisatracurium would most likely be the choice since a drip will often be on for a longer period.

Reversal Agents

So, we've made it through our neuromuscular blocking agents! Now we are going to talk about how we reverse the effect of these drugs. To do this it will be helpful to discuss some of the

anatomy and physiology that these drugs work on before talking about the drugs themselves. Just like we did with the NMBDs, if you understand the underlying physiology, then you will have a much easier time remembering what these reversal agents do and what be aware of with them.

Autonomic Nervous System



This is a busy picture, but I promise you will understand it all by the end of this slide. Don't worry so much about the words yet, just look at the pictures. This is the autonomic nervous system. At a 30,000-foot view. The ANS is responsible for unconscious bodily functions. You don't have to think about making your heart pump, it just happens. You don't have to think about your kidneys making urine, it just happens. The ANS is broken down into two parts: the sympathetic half, and the parasympathetic half. They both work on the same organs, but they work in opposite directions. SNS is your fight or flight system. The SNS supercharges you, while PNS is your rest and digest system. The PNS pacifies you.

So, for the sympathetic system on the right side of the picture. I want you to imagine a scenario where you're walking through the woods, and suddenly you see a huge bear jump out of the woods and it's charging you. What bodily functions are you going to need in that moment? Let's go top to bottom looking at the organs under the sympathetic side. Eyes: You need to be able to visualize as much of your surroundings as possible. The eyes are going to dilate to let as much light in and increase your field of vision. Next is the salivary glands. Would salivating help you fight or run from a bear? Not really, so that function will be dialed back by the SNS. The heart: If you're about to fight or run for your life you need to be delivering more oxygen to your muscles and other organs, so your heart is going to ramp up its rate and contractile strength to increase cardiac output. The lungs: in this scenario, your body is in overdrive and you need as much oxygen as you can get to support it, so the lungs are going to breath faster, open your airways, and take deeper breaths. Stomach: Do you want your stomach and GI tract exerting a bunch of

energy breaking down food in a life or death situation? Not really, so the SNS decreases its activity. Liver: One of its main functions is glucose production and breakdown of glycogen stores for energy. This is helpful for keeping energy levels higher for all the other body parts that are having increased metabolic needs, so it's functions increases. Secretion epinephrine (Epi) and norepinephrine (NE). These are the actual hormones that the SNS uses to signal the organs it wants to communicate with. We will look a little closer at this in our next slide. Bladder & Kidneys: if you're in a life or death situation, do you want your kidneys making a bunch of urine, so you'll have to stop and pee? Not very beneficial in that moment, so it slows down blood flow to the kidneys. Same with the bladder; stopping to urinate isn't very helpful so the detrusor muscle of the bladder relaxes to avoid pressure to urinate.

Now let's walk through the parasympathetic nervous system.

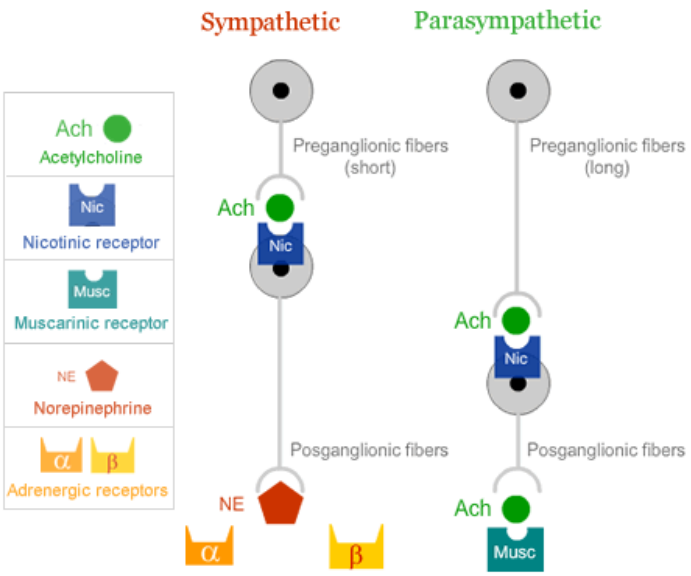
The PNS is the rest and digest system, the exact opposite of the SNS. Think about relaxing on the couch after a delicious dinner, turning down the lights and putting on your favorite show to relax. What functions of the body are working in this scenario? Let's go top to bottom again: The eyes: All you're focus on is the TV at the moment, you don't need to see every possible thing in the room, so the pupils will constrict to reduce light input. The salivary glands: we're digesting a meal right now so they're going to be increasing saliva production. The heart; we're not running or fighting for our lives here, so it's going to slow down its blood pumping. The lungs aren't working overtime right now, we're resting so they're slow down. The GI tract is of course going to be the primary component of food digestion, so it's activity is going to be ramped up. The liver doesn't need to worry about glucose production, we're getting that from the meal that's being broken down in the belly. So, new glucose production is inhibited, but bile is secreted to aid in digestion of your meal. The kidneys and bladder are going to become more active so that we can urinate in peace.

So, why all this information?

Nicotinic and Muscarinic Receptors

Now let's zoom in a little bit here. We're still looking at the ANS but rather than the 30,000-foot view, this is at a cellular level. We still have the SNS and PNS shown separately and with receptors shown as well. -This is a two-step process; the nerves are traveling from spine to organ via two nerves.

So, let's walk through the sympathetic side to start. Starting at the top, our AP is traveling down and releases Ach onto the second nerve. The receptors here are nicotinic receptors, so the AP continues down the second nerve, and here it releases catecholamines, like NE, instead of Ach. NE interacts with adrenergic receptors. These are the alpha and beta receptors that you're familiar with. That's it. Just a couple of steps.



The PNS also has a two-step process that starts the same way, The AP travels from the spine along the first nerve and releases Ach onto a nicotinic Ach receptor. This continues the AP down to the organ, but here is where we see a difference. Instead of adrenergic receptors, we see a muscarinic Ach receptor. These are unique to the PNS. And so, if we increased Ach levels, those molecules will directly stimulate the muscarinic receptors on these organs. This tricks the organ into thinking that the PNS is ramping up its activity. Think back to the previous slide (or even pause and go back to look), what happens to the body when the PNS increases its activity? We see bradycardia, bronchoconstriction, increased salivation, increased GI activity, urine production, etc. We don't stimulate SNS with Ach because we still need the catecholamines to signal the organs directly. The main point here is that increasing Ach levels will directly stimulate parasympathetic activity in the body.

This is important because the way we reverse neuromuscular blockade is by increasing Ach levels in the body.

Acetylcholinesterase Inhibitors

Again, I go through all of that with you because if you understand the underlying physiology, nothing here will catch you by surprise. You won't be memorizing a list of side effects, because these drugs will fit the narrative you already know.

Acetylcholinesterase inhibitors are the drugs we use to reverse NM-blockade, or you can just shorten it to Cholinesterase inhibitors. Remember when we talked about the NMJ, that after an AP signals a muscles fiber with Ach, the Ach is broken down by the enzyme acetylcholinesterase.

These drugs work by stopping the activity of acetylcholinesterase. And if we do that, the overall amount of Ach in the body is going to increase. We're creating Ach without breaking it down. And for our uses, we are thinking specifically of increasing Ach at the NMJ. This works because our NMBDs are competitive antagonists. They compete with Ach at the NMJ for those Ach receptors. With more free Ach in the synaptic cleft at the NMJ, they can knock off the NMBD from the receptors, freeing them to again be reactivated by the Ach there, and cause muscle contraction again.

This is how we reverse neuromuscular blockade today.

The main drugs we use in this category are neostigmine, edrophonium, and pyridostigmine. Neostigmine is by the far the most common one used.

Physostigmine is also in the same class but it crosses the blood brain barrier, so we don't use it.

The Side Effects

What are the side effects of cholinesterase inhibitors? Let's just read through these and we'll talk a little more after. The side effects include:

1) Heart: Bradyarrhythmia, possibly even asystole.
2) Salivary glands: Increased secretions
3) GI Tract: Increase secretions and peristalsis
4) Kidneys/bladder: Stimulates urine production and excretion.
5) Eyes: Miosis (Constriction)
6) Lungs: Bronchoconstriction

Wow, these drugs have a lot of side effects, some of them potentially very dangerous. But take a second and look at this list…What do these side effects have in common?

They are all a result of increased parasympathetic activity. Remember that with drugs we can't tell it to only go to specific body part. They're going to work on every receptor that will accept it., With Ach, we can't limit it to the NMJ to knock off our paralytic drug, it's going to work on the whole body. And as a result, we see these side effects, the major one being significant bradycardia.

So how do we use them safely?

Antimuscarinic Drugs

We must give another type of drug with it called an antimuscarinic drug. They are often called anticholinergics, which is true because they are blocking acetylcholine receptors, but not fully accurate. These drugs don't have any effect on the nicotinic receptors, only the muscarinic receptors. Therefore, antimuscarinic is more accurate.

Also, called parasympatholytic drugs, as they are effectively cutting off the effects of the PNS.

These absolutely must be given with a cholinesterase inhibitor. Otherwise we would see major parasympathetic effects, again, the most problematic of which is the large bradycardia response. Without these antimuscarinic drugs, we'd stop patients' hearts.

There are other benefits: Avoiding severe bronchoconstriction so they can breathe adequately. Reducing secretions is helpful when extubating a patient so they don't get on the vocal cords and cause them to spasm. This also prevents people from going to the bathroom on themselves because we just hammered their GI and urinary systems.

The 3 major drugs in this category are scopolamine, atropine, and glycopyrrolate (Robinul).

We rarely use scopolamine IV because it can cause significant sedation, delaying recovery. Major use is as a transdermal patch for its antiemetic properties. For this reason, we will just continue talking about Robinul and atropine.

So, let's compare and contrast.

	Robinul (0.01 mg/kg)	Atropine (0.02 mg/kg)
Blood Brain Barrier (BBB)	Does not cross BBB Does not cause sedation	Does cross BBB Can cause minor sedation
Time of onset:	Approx. 60 seconds	Approx. 45 seconds
Salivation	Antisialagogue (reduces secretions)	Tachycardia prevents use as antisialagogue
Heart rate	Prevent/reduces vagal-induced bradycardia	Treats bradycardia in emergencies or if Robinul fails

Due to structural differences, Robinul does not cross the BBB while atropine does. This crossing of the BBB is what makes atropine cause minor sedation, although it really is minor, if present at all. Therefore, scopolamine causes major sedation, because it much more readily crosses the BBB. This is part of why we prefer Robinul; since it has most of its effects on the peripheral nervous system rather than also on the central nervous system (CNS). This allows us to reduce the overall side effects.

Time of onset is similar, with Robinul at approximately 1 minute and atropine being a little faster at 45 seconds. This is partially why atropine is better suited for emergency situations: seconds count in emergencies.

Robinul is often given at a low dose to reduce secretions in the patient, as well as to increase heart rate if needed. Atropine can do both things, it hits the heart a lot harder and can often cause more tachycardia than we want, so we don't typically use it as a prophylactic drug.

Side Effects: Antimuscarinics

You will see here as well that these drugs have a lot of side effects. But again, let's read through the list on the left and see what they have in common.

- Tachycardia
- Bronchodilation
- Decreased appetite
- Constipation
- Urinary retention
- Dry mouth
- Blurry vision
- Sedation (not Robinul)

What do they have in common? These are all symptoms of increased sympathetic activity. By cutting off the PNS, we're allowing a stronger reign of the SNS. These two systems are pulling in

opposite directions, so we should dose these patients in such a way that doesn't push them too far in either direction. As mentioned, we can give small doses of these alone, but with the doses we need to reverse paralysis, we need higher dosing.

On the right of the slide you'll see some stronger symptoms that would be indicative of overdose on antimuscarinic drug.

Overdose

- Significant confusion
- Hallucinations
- Significant Tachycardia
- Hot, flush skin
- Fever
- Dizziness

Side Effects: Anticholinergics

This is a mnemonic to help remember the side-effects you would see in an antimuscarinic overdose.

Hot as Hare: refers to the fever/hyperthermia

Dry as a Bone: refers to reducing secretions

Blind as a Bat: refers to pupil dilation resulting in blurry vision

Red as a Beat: Refers to skin flushing

Mad as a Hatter: refers to confusion

Sugammadex (Bridion)

Sugammadex is a very new drug that is changing the game for reversal of neuromuscular blockade. It has been available in Europe since 2008, but the FDA requested more studies before approving it in the US in 2016.

Instead of the indirect reversal we see with neostigmine, this drug directly binds to our aminosteroid compounds, rocuronium and vecuronium, with a slightly higher affinity for rocuronium. Once bound, the paralytic drug can no longer have any effect at the NMJ. And it is then metabolized and excreted.

It is important to note that sugammadex does not work for atracurium or cisatracurium; these will still need to be reversed with neostigmine.

It is truly remarkable how quickly and effectively it works. Within a couple of minutes, depending on how deeply they are blocked at the time of administration, they will be

completely reversed. And if adequately dosed, there should be no lingering paralytic agent still having an effect.

The biggest drawback right now is that it is very new, and as we know, new drugs are expensive. We like to have it as back up in situations where we need to wake a patient up quickly, but we still reserve its use due to cost. But eventually, as cost comes down, it will be the only drug we use.

One interesting side effect is that it can interfere with birth control, so if administered, patients need to be counselled to use other methods of contraceptive for a week after surgery. I don't know how many people are going to be ready for sexual activity within a week of surgery, but who knows?

Why is this important?

- Residual paralysis in PACU is more common than expected.
- As many as 40% of patients who receive NMBDs intraoperatively will still have some amount of blockade when arriving in PACU.
- These patients may be awake and spontaneously breathing, but their muscles still have some weakness.
- This is not because anesthesia providers are being careless, but rather due to limitations in our monitors.
- More prone to episodes of oxygen desaturation, upper airway obstruction, muscle weakness, and a longer stay in recovery.

Why is all of this so important? As PACU nurses, you are the ones who are taking care of these patients immediately after we've given them these drugs. And you all do an awesome job of that. We want you to be rock solid in your grasp on these drugs, because they have the potential to be extremely dangerous if we become cavalier in our handling of them.

Let's touch base on something called residual paralysis, which is exactly what it sounds like; the remaining effects of lingering NMBD in a patient. As many as 40% of patients may some level of blockade when arriving in the PACU. That's no small number. But it's not so obvious. We aren't dropping off one out of every 2-3 patients not breathing. These patients may be awake and breathing spontaneously, but are just not back to their full strength.

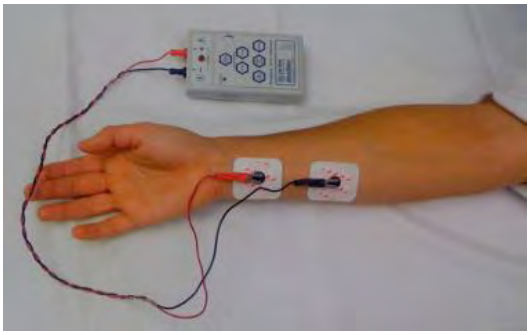
This is not because anesthesia providers are being careless, but rather due to the limitations of our monitors. And we will talk about these monitors in the next couple of slides. They provide very good information, but the readings we get are also somewhat subjective to the provider. It's helpful, but not perfect. And this is where the residual paralysis comes in.

So, what does this look like in PACU? Patients are going to be more prone to desaturation, airway obstruction, use of accessory muscles for respiration, perhaps even complain of feeling weak. And all of this leads to a longer recovery.

You may also see Signs and Symptoms of the reversal agents that we mentioned as well. These drugs may still have lingering effects during recovery.

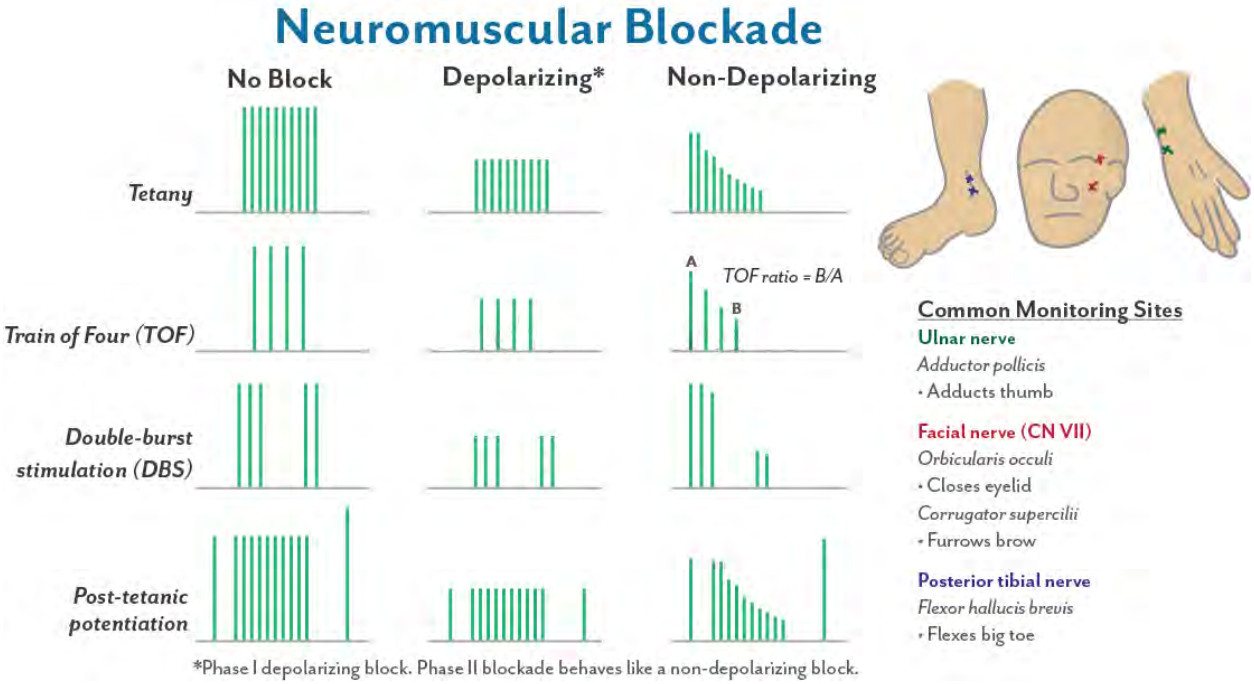
Peripheral Nerve Stimulators

The monitor we use to look at depth of NM-blockade is called a peripheral nerve stimulator AKA a twitch monitor. It simply delivers an electrical stimulus to a nerve causing contraction of a muscle. This picture shows placement at the ulnar nerve, which would cause thumb contraction. The tests we use are called Train of Four and Sustained Tetany, which we will look at in our next slide.



Neuromuscular Blockade

This picture has everything you need to know about twitch monitors.



Look at the right side of the picture. In the top right, we see specifically where we would place our electrodes, and beneath them, we see the color coordinated nerves and motor responses at each site. The ulnar nerve stimulates the Adductor pollicis, which adducts the thumb. The facial nerve stimulates the Orbicularis oculi, which closes the eyelid, and the Corrugator supercilii, which furrows the brow. And the posterior tibial nerve stimulates the flexor halluces brevis, which flexes the big toe.

Let's turn to the graph portion of the picture. Look at the first row, labelled Tetany. In the left column, we see our baseline reading with No Block. This will look like a strong, sustained muscle contraction. You'll notice that depolarizing and non-depolarizing agents have slightly different effects here. The depolarizing agent, or succinylcholine, simply produces a weaker contraction for the duration of stimulation compared to baseline. This is referred to as a Phase I block. Whereas the non-depolarizers have a drop off as the stimulation continues. This is call fade, and is referred to as a Phase II block. It's not until the absence of fade with sustained tetany that we can safely assume full reversal has been achieved.

The Train of Four test is four quick, sequential bursts rather than one long stimulation. But we see the same pattern. The depolarizers simply reduce the strength of contraction without producing fade, while the non-depolarizers do produce fade. Each twitch is weaker than the preceding twitch. And depending on how deeply blocked they are, we can even lose twitches. For surgery requiring relaxation, we usually try to keep them at a reading of 1-2 out of 4. It is possible to achieve 0 out of 4, but this makes it difficult to determine a time until we will get a single twitch back, so we try to always keep at least one twitch.

I mentioned limitations to this monitor earlier so let's talk about those.

- It is difficult to determine exactly what level of fade is present. While we can see and feel the fade of muscle contraction, the AMOUNT of fade is difficult to assign a value to without highly specialized equipment. And the degree of fade plays into muscle strength as much as the presence of fade itself.
- A patient with a train of four reading of 4 out of 4 twitches, can still have up to 75% of acetylcholine receptors blocked. 75% of acetylcholine receptors can still be blocked in someone with four twitches. Therefore, we look to sustained tetany as a better guide for full reversal. Once the presence of fade is gone during sustained tetany, we know the patient is safe to extubate.
- We mentioned in the last slide that larger muscles recover first, while smaller muscles take longer to recover from blockade. The nerve you choose to test will have correlation with other muscles in the body. For example, the facial nerve innervates some larger muscles of the face. This nerve correlates more closely to the diaphragms strength than would the ulnar nerve. However, the nerves of the larynx and trachea that contract those airway muscles, are very small compared to the diaphragm. So, if monitoring the facial nerve, consider that even if you have a strong train of four reading and the patient is breathing, the airway muscles may still be weak. The ulnar nerve correlates a lot more closely with the airway muscle strength. We must consider this when recovering from blockade.

Testing for muscle strength

Now, you most likely will not be using twitch monitors very often. Although it's not unheard of, especially in the occasional patient that comes to PACU still intubated and ventilated. So how can you evaluate a patient's muscle strength without a twitch monitor. These are some simple tests you are probably familiar with that can be a good guide.

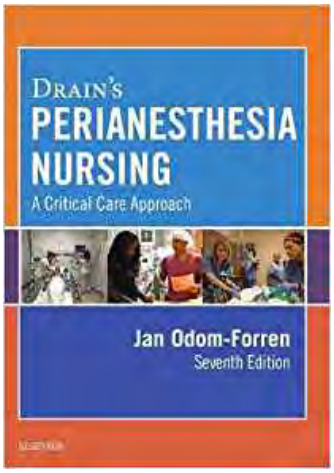
I put sustained head or leg lift first because this is the gold standard for reversal of paralytic. However, it can be difficult to get a patient that is groggy to sustain a head lift even if they are strong enough to do so. But we have other options, such as:

- Sustained head or leg lift for 5 seconds (gold standard)
- Opening eyes
- Strong hand squeeze
- Protrusion of the tongue
- Purposeful movement
- Strong cough
- Sustained bite on tongue blade
- Ability to swallow

These are some quick and easy ways to determine someone's strength. If the patient is not performing well on these, then you could consider the use of a nerve stimulator.

Thank you!

Thank you very much for your attention and I hope this presentation has been beneficial and educational for you. If you would like more detailed information on all the topics we discussed, I'd like to recommend Drain's Perianesthesia Nursing textbook. It goes into greater detail about a lot of these things like nerve stimulators and it also covers things like how these drugs work differently on patients with neuromuscular disorders and some other factors that affect duration of blockade.



Chapter 23 is the one you'll want.

Thank you again.

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