

Episode 66: Neuromuscular Blockers

On this episode: Dr. Jed Wolpaw

This is an overview of neuromuscular blockers including how they work, how to use them, and what their adverse effects are. Reversals are not covered in details. Check the [sugammadex episode](#) or in a future episode for more details on reversals.

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Happy New Year!

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History:

- 1942: First clinical use of neuromuscular blocker. D-tubocurarium in surgery, until the six-fold increase in mortality was realized.
- 1952: First use of succinylcholine, then different NMB

Postsynaptic acetylcholine receptors

- Key to reversal with glycopyrrolate (glyco) or neostigmine (neo)
 - o Nicotinic ACh receptors at neuromuscular junctions
 - o Muscarinic ACh elsewhere
 - o Glyco is antimuscarinic, so ↑ ACh everywhere but blocks only the muscarinic receptors, and not nicotinic receptors
- Acetylcholine (ACh) activates receptors via ion channel
 - o Two ACh must bind simultaneously to open channel
 - o Non-depolarizing blockers need only one to block
- Only depolarizing blocker is succinylcholine (sux)
 - o Prolongs potential at endplate → desensitizes junctional receptors
 - o Inactivates Na channel, ↑ EFFLUX of potassium → hyperpolarization → can't cause action potential → can't contract muscle

Fetal nicotinic receptors

- Can proliferate outside neuromuscular junction
- Can spread if the junction is not innervated, such as with an injury or burn
- Resistant to non-depolarizers, and more sensitive to sux → stay open longer → more K efflux
→ can get extreme hyperK
 - o Caution with conditions that cause proliferation of fetal nicotinic receptors

Presynaptic acetylcholine receptors

- Positive feedback when stimulated → more ACh available at endplate
- Sensitive to non-depolarizer, but not sux
 - o Train of fours (ToF) fade occurs for non-depolarizers
 - First twitch uses up some ACh at motor end plate
 - Prejunction blocked → no more action potential sent to release ACh at endplate → can't mobilize extra ACh → weaker successive twitches
 - o Sux doesn't act on these presynaptic receptors, so don't typically see the fade
 - Doesn't stop the increased action potential to endplate from presynaptic stimulation
 - Twitches should all be the same, unless Phase 2 block..

Why use NMB?

- Makes intubation easier
- Reduce rate of vocal cord damage, difficult intubations, and complications

Succinylcholine

- 2 ACh molecules

Dosing

- ED95 0.5mg/kg
- 1mg/kg
 - o Total relaxation in 60 seconds

- ↑ K by 0.5mEq/mL, assuming all else normal
- Total recovery ~ 10 minutes (~90% strength back)
 - Assuming normal pseudocholinesterase (which breaks it down)
- Reducing activity of pseudocholinesterase by 80% only prolongs for few minutes
 - Not very clinically significant
 - Activities like liver disease, pregnancy, old age, MAO_i, chemotherapeutic drugs, or esmolol
- If high enough or repeated dose, can cause phase 2 block
 - Dose – 5mg/kg?
 - Phase 2 = acting like non-depolarizing agent, so see fade
- Sux given after reversal for non-depolarizing agent can ↑ duration of sux block (even tripled)
 - It takes about 90 minutes for pseudocholinesterase to recover from neostigmine
 - Sux can last a lot longer after reversals given

Abnormal pseudocholinesterase

- **Dibucaine test:** Local anesthetic that inhibits normal pseudo. by ~ 80%, but abnormal pseudocholinesterase types will be less inhibited
- | Genotype | % of Pseudo. Inhibited | Sux Prolongation |
|---------------------|------------------------|------------------|
| <i>normal</i> | 80% | |
| <i>heterozygous</i> | 50-60% | 1 to 2x |
| <i>homozygous</i> | 20% | Up to 8 hours |
- % inhibited = Dibucaine #
 - If patient doesn't get up after a short case, consider this condition as a diagnosis of exclusion

Cardiac effects

- People with higher vagal tone, like pediatrics, more susceptible
 - Atropine as pretreatment to attenuate potential bradycardia.
- Brady more common after 2nd dose of sux
- Tachycardic after high doses

Risk factors for hyperkalemia

- Studies show that patients with severe metabolic acidosis or abdominal infection can get more extreme hyper K from sux
 - Possibly from gut. Still experimental, thus not tested
- Trauma patients ↑ risk
 - Susceptible 1 week after, lasting up to 60 days
- Nerve injury
 - Loss of nerve innervation, hemiplegia, muscular dystrophy, Guillain-Barré
 - More fetal nicotinic receptors
 - Risk starts as early as 48 hours after injury and can last 2+ years

Increased pressures

- ↑ Intraocular pressure
 - Transient last about 6 injuries
 - Well tolerated except for open globe
- ↑ Gastric pressure
 - Prevented by being given a defasciculating dose first
 - 5mg of rocuronium 1-2 min before sux, can prevent fasciculation and rise in gastric pressure
 - Controversial due to potential side effects: weakness, distressing, inability to protect airway. Follow local protocol
- ↑ Intracranial pressure

Muscles

- Myalgia
 - o Unclear but some people found defasciculating dose to be helpful
 - o Some studies show up to 90% get myalgia
 - o More common in certain populations such as outpatient surgeries, healthier people, women, active
- Masseter spasm
 - o If isolated, can be early sign of MH, but usually not. Other signs more compelling like hypercapnia, tachycardia, metabolic acidosis, fever..

Non-depolarizing NMB

- 2 classes
 - o Steroidal (most often used)
 - Vecuronium
 - Rocuronium
 - Pancuronium
 - o Tetrahydroisoquinoline derivatives
 - Atracurium
 - Cisatracurium
 - Mivacurium
- Sugammadex
 - o Will reverse former group, not latter

Cisatracurium

- Likely used for renal failure
- Primarily eliminated by Hoffman-elimination
 - o Essentially just falling apart, doesn't require organ or enzyme
 - o Cleavage of carbon-nitrogen bond
 - o Temp or pH dependent
- Doesn't cause histamine release, unlike atracurium

Pancuronium

- Not used much
- Vagolytic and inhibitor of butyrylcholinesterase (aka pseudocholinesterase)
 - o Prolongs sux if used after pancuronium

Rocuronium and Vecuronium

- 5-10x less potent than vecuronium, thus intubating concentration
 - o **Roc:** ~0.6 mg/kg
 - Rapid: 1.2 mg/kg
 - o **Vec, Cis:** 0.1mg/kg or less
- Induction dose
 - o **Roc:** 50mg
 - Typical dose in vial
 - o **Vec:** 10mg
 - Typically reconstituted to this amount

Dosing

- Supplemental: go low
 - o **Roc:** 0.1 mg/kg
 - o **Cis, Vec:** 0.02 mg/kg
- Titrate infusions
 - o **Roc:** 10 mcg/kg/min

- Vec: 1 mcg/kg /min
- Decrease if you want twitches
- (selected and simplified)

NMB	ED95 (mg/kg)	Induction (mg/kg) [duration in min]	Rapid (mg/kg) [duration in min]
Rocuronium	0.3	0.6 [30-45]	1.2 [70-80]
Vecuronium	0.05	0.1	0.2 [17-18]
Cisatracurium	0.05	0.1 [45-50]	0.2 [70-80]
Pancuronium	0.05	0.1	[100+]
Mivacurium		0.2-0.25	[15-20]

Onset

- (selected and simplified)

NMB	Dose (mg/kg)	Onset (min)	RSI Onset (min)
Succinylcholine	1	1	
Rocuronium	0.6	1.5	1
Vecuronium	0.1	2.5	
Cisatracurium	0.2	2.7	2

Duration

- Prolonged
 - Volatiles [des > sevo > iso], not clinically significant
 - Hypothermia
 - 10-15% ↓ for every degree below 36
 - Most with cis and atrac due to Hoffman (colder = slower)
 - Magnesium
 - Opposite of calcium
 - Lithium
 - IV local anesthetic
 - If on drip, check dosing!
- Shortened
 - Long term anti-epileptics – resistant to NMB
 - Vec clearance can be doubled for pts on carbamazepine
 - Steroids antagonize NMB

Elimination

NMB	Elimination
Succinylcholine	Pseudocholinesterase
Cisatracurium	Mostly Hoffman, unclear renal
Vecuronium	50% liver/biliary, 50% renal
Rocuronium	75% liver/biliary, 25% renal
Mivacurium	Pseudocholinesterase

Adverse effects

- Atracurium, mivacurium: histamine release → hypotension, bronchospasm
- Pancuronium: tachycardia
- Most likely cause of anaphylactic reaction? **NMB**, not antibiotics
- Sux dose after defasciculating dose of roc or vec? ↑ dose (eg 1.5 instead of 1)

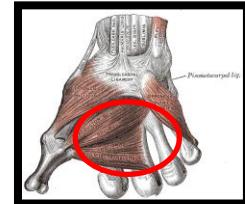
Specific demographics

Pediatrics	<ul style="list-style-type: none"> - Careful with sux: Pretreat with atropine - Avoid because if young boy has unsuspecting muscular dystrophy, might expect cardiac arrest from hyperkalemia, develop rhabdomyolysis - Children, not infants, need higher dosing of steroidial nondepolarizing agents
Older age	<ul style="list-style-type: none"> - ↓ hepatic/renal clearance → ↑ duration of nondepolarizing blockers
Obesity	<ul style="list-style-type: none"> - Prolonged if dosed on body weight - Should dose based on ideal, because muscle mass is similar
Renal failure	<ul style="list-style-type: none"> - Major effect on vec and roc → prolong - Not so much on cis
Liver	<ul style="list-style-type: none"> - Cirrhosis ↑ volume of distribution → shorten duration - Impaired liver function → prolong duration - Studies show that small dose of vec can shorten duration in liver failure, but large dose can last longer - Severe liver disease can reduce amount of pseudocholinesterase, so prolong mivi and sux duration of action
ICU	<ul style="list-style-type: none"> - Worsen neuropathy? Polyneuropathy. ICU myopathy - Avoid NMB if possible - Use cis if needed, such as for ARDS or intubation <ul style="list-style-type: none"> o Study showed advantage and mortality benefit to NMB in severe ARDS, but lots of places use vec instead due to costs

Twitches

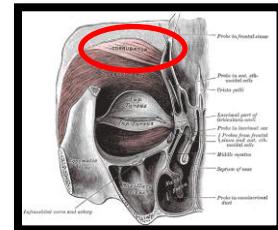
Adductor pollicis

- Twice dose to paralyze diaphragm vs adductor pollicis muscle
 - o It makes sense if no twitch in thumb, but diaphragm is moving
- Laryngeal muscle also more resistant than adductor pollicis
 - o It makes sense why we might see good twitches on thumb but still can't protect airway
- KEY
 - o Patient who can breathe with tube in place doesn't mean they can protect their airway when tube is out. You shouldn't think "*Oh look tidal volumes are their own, so they don't need reversal.*" Patient might have capable diaphragm that can pull good tidal volumes but still unable to protect airway and stop from obstructing due to weak upper airway. So if you see good tidal volumes, disconnect from monitors and wheel to PACU, then realize patient's CO₂ is 120, it's because patient is obstructed!



Corrugator supercilii

- Common to use corrugator supercilii muscle
 - o Above orbicularis oculi
 - o Similar depth, onset, recovery as larynx and diaphragm
 - o Recovery much sooner than upper airway muscle → be more careful than when using thumb!
 - o But don't need to wait until all twitches for optimal paralysis of larynx.
 - o If obvious weakening of adductor pollicis, which is more sensitive than corrugator, then probably fine to intubate



Reversal

- Before sugammadex was neostigmine and glycopyrrolate
 - Neostigmine
 - o Acetylcholinesterase inhibitor → more ACh to flood junction → competitively inhibit NMB → recover
 - Use glyco to block effects on gut and heart so action only at nicotinic

Myth: If given cis, don't need reversal

- Yes it will go away on its own, so will roc and vec eventually. Point is that you can use in renal failure patients. Can't use sugammadex.

Dose

- Neostigmine: 70mcg/kg up to 5mg
 - Glycopyrrolate: 0.1 to 0.15 mg/kg
 - Commonly give 5mg of neo (5 cc) and match volume with glycol (5 cc), which is 1mg of glycol
 - o A bit of overdose of glycol so some tachycardia. Generally fine but if you want to avoid, reduce dose of glyco, like 0.7 or 0.8
 - Alternatively, acetylcholinesterase inhibitor such as pyridostigmine, with atropine
 - o Onset matches up like neo/glyco
 - Always better to err on side of using a reversal. If you can't see/feel fade, but are strong twitches, don't trust it! Still give at least $\frac{1}{2}$ dose. There's ↑ rates of respiratory complications for those that didn't receive reversals. Of course, if it's been like 10 hours, or have accelerometer that shows 90% recovery, then fine. Follow protocols! **Don't assume** that movement, head lift, no fade, or breathing on own, equate to full recovery and safe to extubate without reversal.

How do you reverse paralytics? Is this how you use neuromuscular blockers? What are your thoughts?

Review Questions

Link jumps to appropriate section

1. [A denervated junction will be more sensitive to which NMB?](#)
2. [How do these receptors explain no fade in Phase 1 of Succ?](#)
3. [How do you interpret dibucaine 50? How does this compare to dibucaine 80?](#)
4. [Why would you still protect airway despite good twitches on thumb?](#)
5. [If arms are tucked, where else would you check for twitches?](#)

References

- Miller's Anesthesia 7th edition: Chapter 29: Pharmacology of Muscle Relaxants and Their Antagonists. Naguib M and Lien C.
- [Rocuronium vs succinylcholine for rapid sequence induction intubation.](#)
- [Neuromuscular blockade: what was, is and will be](#)
- [Reversal of neuromuscular block](#)

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