AN UPDATE ON MONITORING AND ANTAGONISM OF NEUROMUSCULAR BLOCKADE

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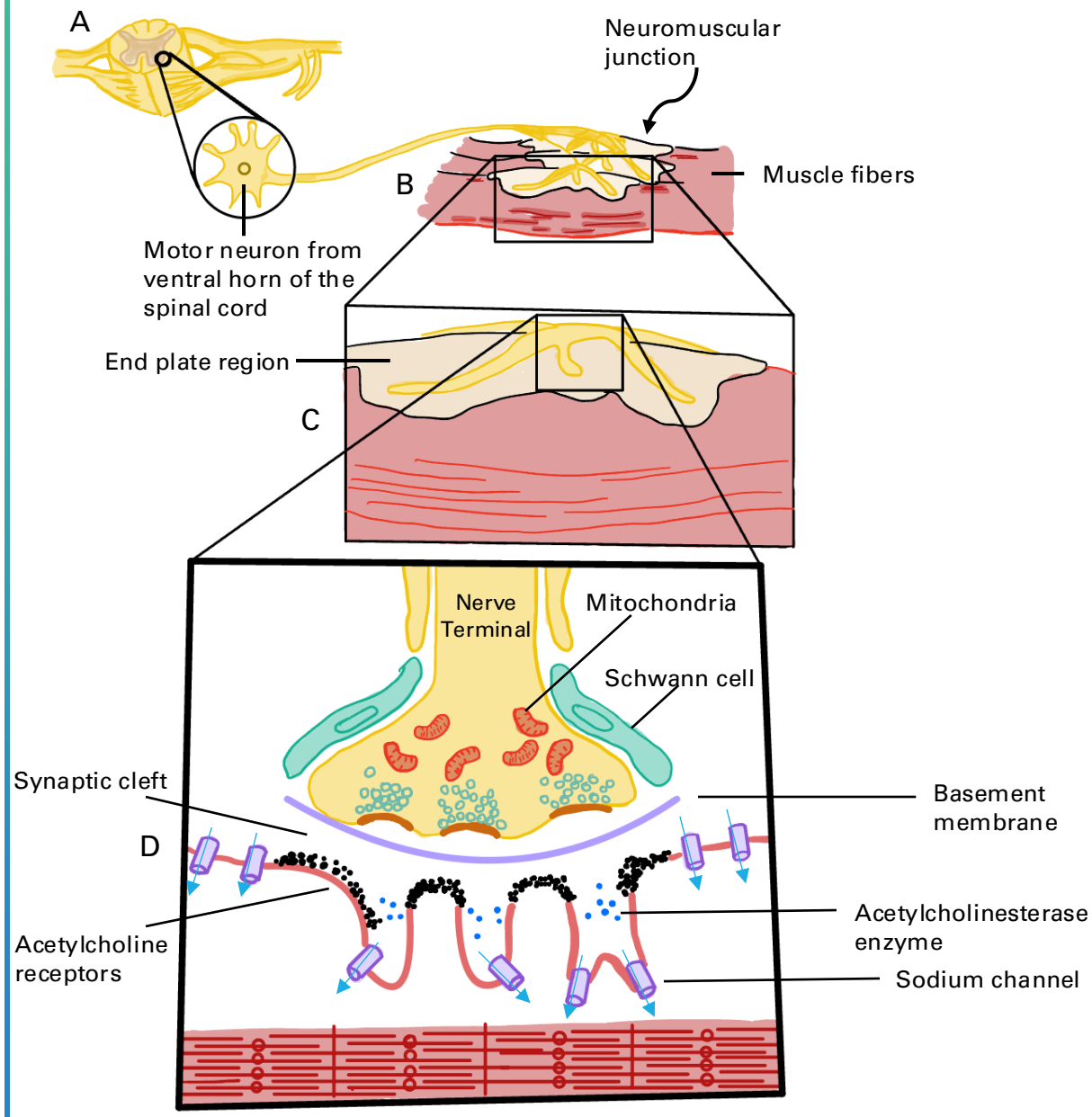
Structure of the adult neuromuscular junction (NMJ)



This schematic shows the three cells that constitute the synapse: the motor neuron (nerve terminal), muscle fiber, and Schwann cell.

A) The motor neuron originates in the ventral horn of the spinal cord

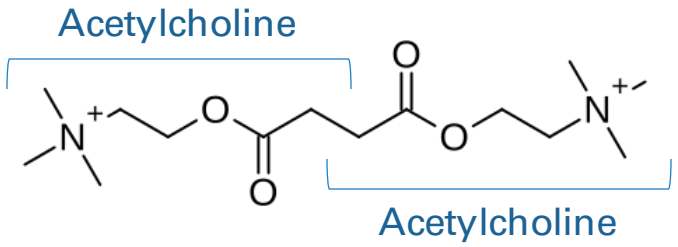
B) As the nerve approaches muscle fibers it divides into branches that innervate many individual muscle fibers

C) Each muscle fiber receives one synapse. The motor nerve sheds its myelin sheath and further divides into pre-synaptic boutons to terminate on the surface of the muscle fiber

D) The nerve terminal is covered in Schwann cells, and it contains vesicles which contain acetylcholine (ACh). The muscle surface has areas on each fold that contain ACh receptors. Sodium channels are also found here and help propagate the signal.

Depolarizing neuromuscular blocking (NMB) agent

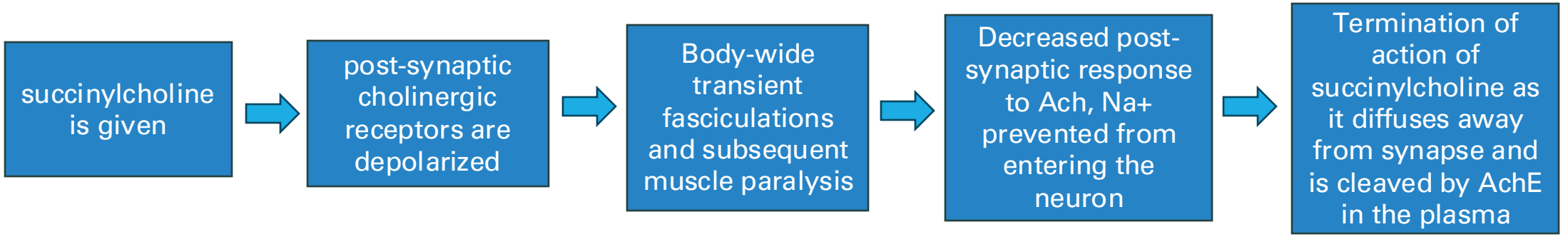
- **Succinylcholine** is an agent composed of two acetylcholine molecules linked together that is more resistant to breakdown by enzyme acetylcholinesterase (AchE)
  - intubating dose 1 mg/kg; time to max effect ~70 sec
- Causes depolarization, motor end plate remains depolarized, Na+ channels inactivated and nAchR become desensitized (Phase I block); in one study the 1mg/kg intubating dose resulted in time to 90% twitch recovery of ~9.3 min
- If repeated doses given, **Phase II block** can happen with a fade seen in the TOF response just like the competitive block seen in nondepolarizing NMBs
- Succinylcholine is hydrolyzed by plasma butyrylcholinesterase so patients with AchE insufficiency can have prolonged blockade and Phase II block with even one dose



Structure of succinylcholine

Vial of succinylcholine

Special Considerations with Succinylcholine Use



Side effects:

- **Increased serum potassium** (usually 0.5 mEq /L) but this effect is more concerning when the patient has a disease pathophysiology that upregulates immature Ach receptors leading to an exaggerated response (*prolonged immobility, spinal cord injury, myelopathies etc)*
- **Bradycardia**, especially in children (*pediatric anesthesiologists like to have atropine at the ready when using succinylcholine)*
- Masseter muscle spasms (trismus)
- **Muscle soreness** even in absence of fasciculations (pre-treatment with NSAIDs can help)

Contraindications to use:

- Malignant hyperthermia
- Reduced plasma cholinesterase (leading to prolonged paralysis)
- Burns or trauma within 72 hours (due to hyperkalemic rhabdomyolysis caused by upregulated Ach receptors)
- Muscle myopathies/neuromuscular diseases

You are taking care of a patient with a BMI of 55. Which of the following properties is seen in this patient that would help explain the pharmacokinetic changes with succinylcholine use in this patient population?

A) Decreased extracellular fluid

B) Increased amount of butyrylcholinesterase

C) Decreased residual volume

D) Increased number of neuromuscular junctions

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This topic was identified as a Gap in Knowledge on the 2015 ITE

Obesity is defined as BMI > 30 (and morbid obesity with BMI > 40), and compared to patients with similar age, height and other characteristics, obesity is associated with increased lean body weight and fat which alter volume of distribution of medications. For succinylcholine, the average dose is 1.0 mg/kg based on total body weight. The level of plasma pseudocholinesterase (aka butyrylcholinesterase) activity as well as volume of extra-cellular fluid determine duration of action for succinylcholine. In non-obese patients, TBW = IBW however in morbid obesity, TBW > IBW and the activity of pseudocholinesterase increases leading to potential under-dosing if dosing is based on IBW. Although there is still some variability in dosing in clinical practice.

Non-depolarizing Neuromuscular Blocking Agents

- competitive AchR antagonists and prevent Ach from binding the nAchR and results in the motor endplate not initiating or propagating an action potential
- classified by their chemical structure: steroidal (rocuronium, vecuronium, pancuronium) and benzylisoquinolinium (mivacurium, atracurium, cisatracurium)
  - rocuronium intubating dose 0.6 mg/kg onset 60-90 sec, RSI dose 1-1.2 mg/kg [excreted unchanged in bile, 30% renal elimination]
  - vecuronium intubating dose 0.08-0.1 mg/kg onset 60-90 sec, RSI 0.1-0.2 mg/kg [liver metabolism 70-80%]
  - cisatracurium intubating dose 0.15-0.2 mg/kg onset 90-120 sec, eliminated via organ independent Hoffman degradation [metabolites do undergo metabolism via liver/kidneys but no clinical significance has been noted]
- do not cause a conformation change in the nAchR. Via constant dissociation/re-association of these agents with the nAChR, a high enough Ach concentration can eventually favor Ach binding to its receptor, re-initiating motor function

You are taking care of a patient who was just started on phenytoin outpatient. You give the patient rocuronium. Do you expect this to change your patient's response to rocuronium? Would your answer change if phenytoin was a chronic medication?

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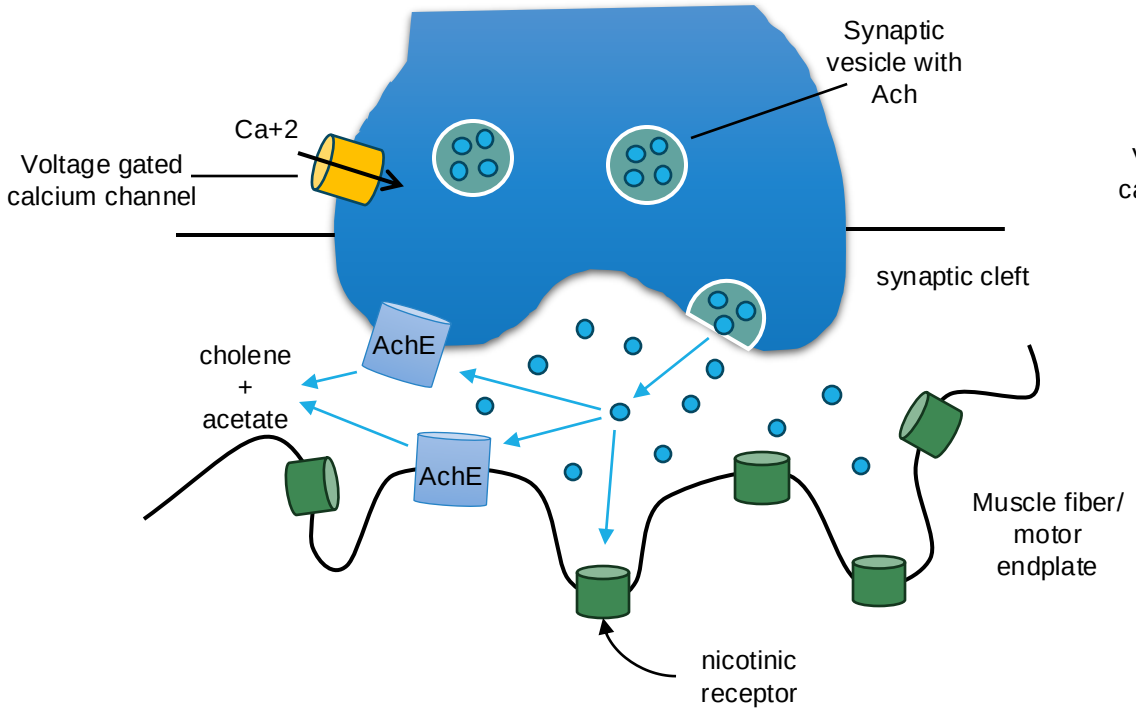
- Acute phenytoin use would **potentiate neuromuscular blockade** with rocuronium
  - Mechanism is not entirely understood but thought to be due to an acute reduction of stimulus induced Ach release from prejunctional neuron
- Chronic phenytoin would **antagonize neuromuscular blockade** with rocuronium
  - Many possible mechanisms including:
    - increased post-synapse Ach R density due to weak neuromuscular blocking properties of phenytoin
    - Increased metabolism via CYP450 enzyme induction (remember that rocuronium and other aminosteroid NMBs rely on hepatic metabolism, which may explain why there is no clear effect with the benzylisoquinolines which undergo hepatic-independent Hofmann elimination and ester hydrolysis)

Effect of various agents on the duration of action of non-depolarizing NMBs

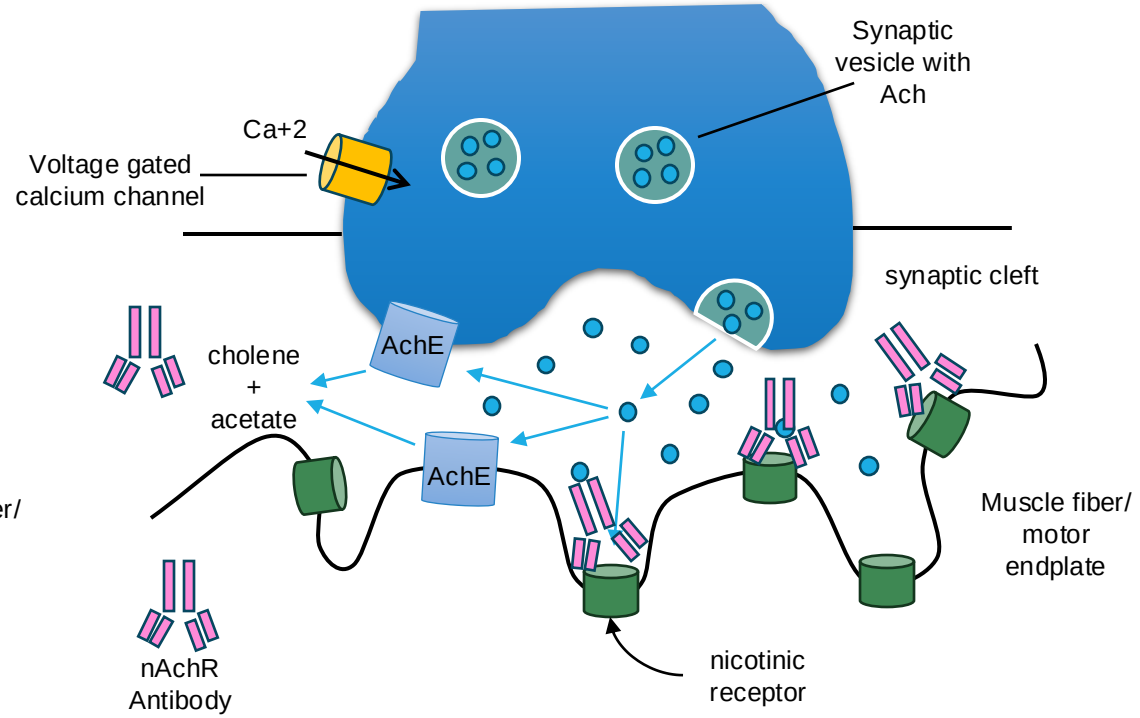
Medication	Effect on duration of blockade
Combining two nondepolarizing NMBs	Same class has additive effect Different classes have synergistic effect
Inhaled anesthetics	Potentiation, with desflurane having the most profound effect > sevoflurane > isoflurane > nitrous oxide
Antibiotics (aminoglycosides, clindamycin, polymyxins, tetracyclines)	Potentiation
Anticonvulsants (phenytoin and carbamazepine)	Acute: potentiation Chronic: Attenuation
Lithium	Potentiation
Local Anesthetics	Potentiation

Pathophysiology of Myasthenia Gravis

Normal neuromuscular junction



Neuromuscular junction in Myasthenia Gravis



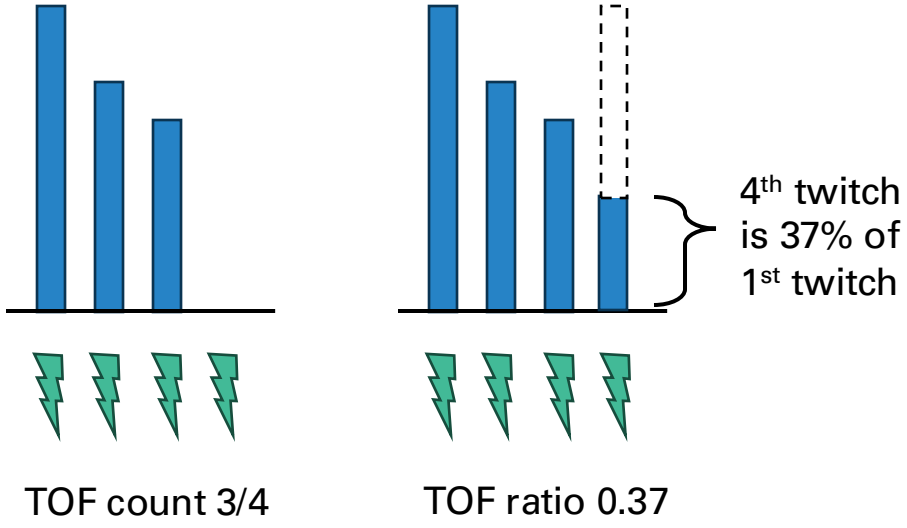
Weakness in MG is caused by autoimmune mediated loss of pos-synaptic proteins of the NMJ, with 85% of patients having auto-antibodies against nAchR (others include antibodies to MuSK, LRP4, agrin etc). nAchR antibodies block Ach from binding to the receptor and incite complement-mediated nAchR destruction which ultimately results in decreased motor end-plate potential amplitude and failure to start muscle fiber contraction.

Myasthenia Gravis (MG) and Non-depolarizing NMB

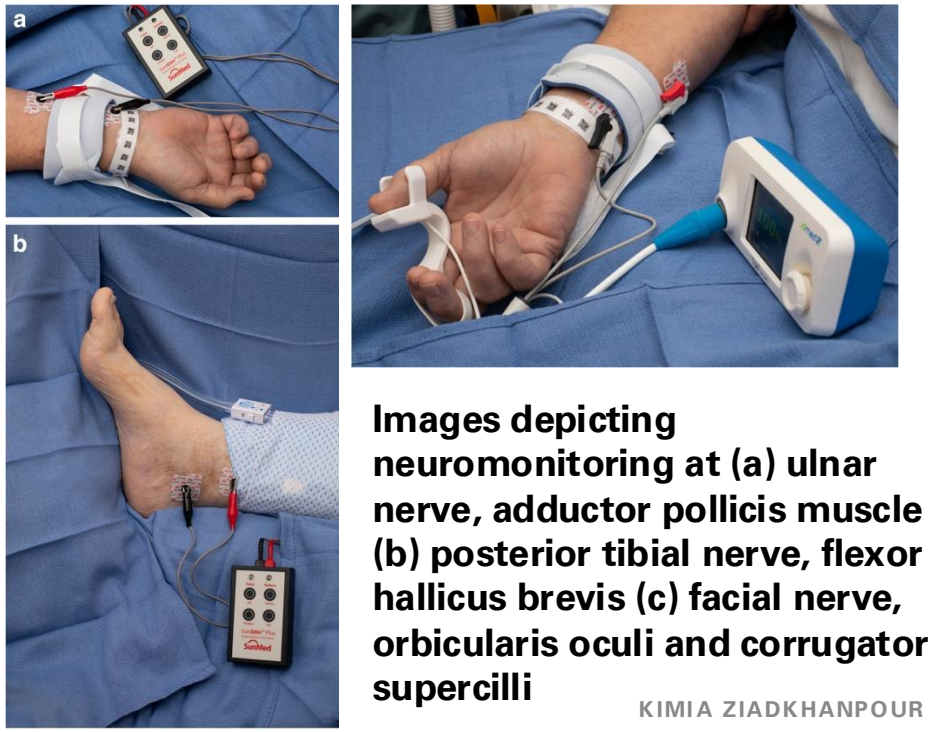
- MG results in a decrease in post-synaptic AchR in the neuromuscular junction
- These patients are **sensitive** to neuromuscular depressant affects of inhaled anesthetics and to nondepolarizing agents
- Still, non-depolarizing agents are preferred (in smaller doses), as MG patients are **resistant** to depolarizing NMBs due to decreased number of Ach receptors at the post-synaptic site
- Sugammadex should be used for reversal, as anticholinergic agents can result in cholinergic crisis (symptoms include diarrhea, blurry vision, increased salivation and lacrimation)

Monitoring Neuromuscular Blockade

- Several patterns of stimulation are used to assess the depth of blockade, train of four (TOF) being the most common
- TOF ratio: delivers 2-4Hz stimulus 4 times, and the ratio (in terms of amplitude) between the 4th and 1st twitch responses is possible with quantitative monitors
  - Visually, we cannot perceive fade until the TOF ratio is below 0.4.
- TOF count: simple count of muscle twitches after a TOF stimulation is applied
  - Correlates with a degree or receptor blockade, at TOFC =4, 70% of nAchR are still blocked



Train of four examples. The bars represent magnitude of twitch response. Lightning bolts represent stimulus applied from the neuromuscular monitor



Images depicting neuromonitoring at (a) ulnar nerve, adductor pollicis muscle (b) posterior tibial nerve, flexor hallicus brevis (c) facial nerve, orbicularis oculi and corrugator supercilli

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These images obtained from Open Access Journal: Renew, J.R., Ratzlaff, R., Hernandez-Torres, V. *et al.* Neuromuscular blockade management in the critically Ill patient. *j intensive care* **8**, 37 (2020). https://doi.org/10.1186/s40560-020-00455-2

Neuromuscular Blocking Agents: Recovery

- Residual neuromuscular blockade is an under-recognized phenomenon; a 1979 study of 79 patients concluded that 42% of patients dropped off in the PACU had residual blockade [definition of residual blockade used in this paper was TOF ratio <0.7]
- ASA warns against using clinical assessment alone to prevent residual neuromuscular blockade (as this is an insensitive method), instead recommends quantitative measurement with train of four > 0.9 before extubating [adductor pollicis muscle >> eye muscles]
- Sugammadex should be used at deep, moderate, and shallow depths of neuromuscular blockade when rocuronium or vecuronium have been used
- If neostigmine is to be used for reversal, depth of blockade should be minimal
- If cisatracurium is used, wait for minimal neuromuscular blockade, then reverse with neostigmine and if not using quantitative methods, wait 10 mins before extubating

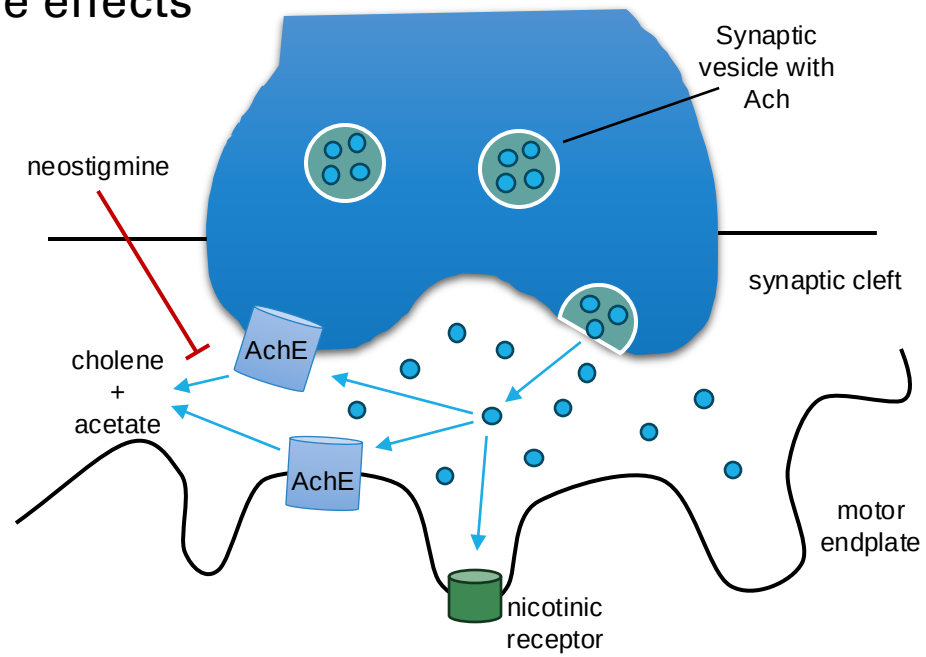
Depth of blockade	Peripheral Nerve Stimulator and Qualitative Assessment	Quantitative monitor
Complete	Post tetanic count = 0	Post tetanic count =0
Deep	Post tetanic count ≥ 1; TOF = 0	Post tetanic count ≥ 1; TOF =0
Moderate	TOF count = 1-3	TOF count = 1-3
Shallow	TOF count =4, TOF fade present	TOF ration <0.4
Minimal	TOF count = 4, TOF fade absent	TOF ratio = 0.4-0.9

Reversal of Aminosteroidal nondepolarizing NMBs

- Sugammadex is a modified gamma-cyclodextrin with 8 side chains that contain negatively charged carboxyl groups.
- Has a deep hydrophobic cavity that enhances binding to rocuronium > vecuronium > pancuronium
- Once the NMB is encapsulated, a gradient is created that favors the molecule moving away from the neuromuscular junction thereby inactivating the effects of rocuronium
- **Special Considerations**
  - Potential interference with hormonal birth control, and patients should be counseled to use backup methods of birth control when given sugammadex
  - Society for Obstetric Anesthesia and Perinatology recommends against use of this in early pregnancy due to progesterone binding capability of sugammadex (although literature is insufficient)
- **Side effects:**
  - Dose dependent bradycardia, treated with vasopressors if needed
  - Anaphylaxis within first few minutes of administration
  - No muscarinic effects

Reversal of NMB with Neostigmine

- Neostigmine is an AchE inhibitor that increases Ach at the NMJ and therefore allows Ach to outcompete the non-depolarizing blocking agents
- With max doses of neostigmine, AchE is fully inhibited and increasing the dose does not hasten full recovery. Therefore, it is recommended to give this form of reversal when the patient has at least 2 twitches, and the more twitches the better.
- Even with 2-4 native twitches, wait 15 mins after administering neostigmine before extubation
- Dose neostigmine: 0.03-0.05 mg/kg; given along with glycopyrrolate 10 mcg/kg to mitigate undesirable muscarinic side effects



A 45-year-old woman undergoing laparoscopic hysterectomy is given rocuronium. At the end of her surgery, her TOF ratio is greater than 0.9, and then she is given glycopyrrolate and neostigmine in the appropriate doses. What side effect may be experienced by the patient?

A) Bradycardia

B) Diarrhea

C) Increased secretions

D) Respiratory weakness

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D) If neostigmine is given when neuromuscular function has been fully recovered (TOF ratio > 0.9), it has been shown that there can be paradoxical upper airway weakness. This is seen as decrease in tone in the upper airway dilator muscles as well as impaired diaphragm function.
Underlying reasons for this remain unclear but may be due to desensitization of Ach receptors due to high levels of circulating acetylcholine.

Take Home Messages

- There are two categories of neuromuscular blocking agents: non-depolarizing vs depolarizing
- Succinylcholine is depolarizing, and it is often still used in rapid sequence intubation due to its quick onset. Anesthesiologists must consider other options in pathophysiologic states that render its use potentially unsafe
- Residual neuromuscular blockade has been previously described in the PACU setting; it is imperative to monitor level of blockade throughout the case, ensuring TOF ratio of at least 90%
- Our guidelines recommend against clinical assessment alone to avoid residual blockade; sugammadex is the current recommended mode of reversal for deep, moderate and shallow depths of neuromuscular blockage by rocuronium or vecuronium
- When neostigmine is used for reversal in states of minimal neuromuscular blockade depth, glycopyrrolate should be used to minimize muscarinic side effects

References

- Martyn, Jeevendra, and Malin Jonsson Fagerlund. *Miller's Anesthesia*, 9th ed., vol. 1, Elsevier, Philadelphia, PA, 2020, pp. 333–353, Accessed 12 Nov. 2024.
- Aaron F. Kopman, Bledi Zhaku, Kane S. Lai; The "Intubating Dose" of Succinylcholine: The Effect of Decreasing Doses on Recovery Time. *Anesthesiology* 2003; 99:1050–1054 doi: https://doi.org/10.1097/00000542-200311000-00007
- Connor, C. W., Cullen, B. F., Holt, N. F., Nathan, N., Ortega, R. A., Sharar, S. R., & Stock, M. C. (2024). Barash, Cullen, and Stoelting's clinical anesthesia (Ninth edition.). Wolters Kluwer.
- Schreiber, J. U., Lysakow ski, C., Fuchs-Buder, T., & Tramèr, M. R. (2005). Prevention of succinylcholine-induced fasciculation and myalgia: a meta-analysis of randomized trials. Anesthesiology, 103(4), 877–884. https://doi.org/10.1097/00000542-200510000-00027
- J. Ingrande, H. J. M. Lemmens, Dose adjustment of anaesthetics in the morbidly obese, *BJA: British Journal of Anaesthesia*, Volume 105, Issue suppl_1, December 2010, Pages i16–i23, https://doi.org/10.1093/bja/aeq312
- Wright, P. M., McCarthy, G., Szenohradszky, J., Sharma, M. L., & Caldwell, J. E. (2004). Influence of chronic phenytoin administration on the pharmacokinetics and pharmacodynamics of vecuronium. *Anesthesiology*, *100*(3), 626–633. https://doi.org/10.1097/00000542-200403000-00024
- Barash PG, et al. *Clinical Anesthesia.* Ch. 21: Neuromuscular Blocking Agents: Individual Nondepolarizing Agents. 8th Edition.
- Renew, J.R., Ratzlaff, R., Hernandez-Torres, V. *et al.* Neuromuscular blockade management in the critically Ill patient. *j intensive care* **8**, 37 (2020). https://doi.org/10.1186/s40560-020-00455-2
- https://pubs.asahq.org/anesthesiology/article/138/1/13/137379/2023-American-Society-of-Anesthesiologists
- Statement on Sugammadex during Pregnancy and Lactation. Society for Obstetric Anesthesia and Perinatology. https://www.soap.org/assets/docs/SOAP_Statement_Sugammadex_During_Pregnancy_Lactation_APPROVED.pdf (Accessed on June 04, 2024)
- Gropper M, et al. *Miller's Anesthesia.* Reversal (antagonism) of neuromuscular blockade. 9th edition. Ebook. Pages 840-852.

A more detailed list of references can be provided upon request