Neuromuscular Blocking Agents

Succinylcholine

- Structure = 2 adjoined ACh molecules!
- Mechanism of action is by ACh receptor activation and prolonged muscle depolarization.
- Dose: 1 to 1.5 mg/kg for intubation.
- Onset within 30-60 seconds and duration ~10 minutes depending on dose.
- Elimination by diffusion away from NMJ and metabolism by pseudocholinesterase (a.k.a. plasma cholinesterase)
  - Atypical pseudocholinesterase (genetic defect) can significantly prolong SCh block; enzyme activity measured by the "dibucaine number":
  - Normal = 80 (i.e. dibucaine inhibits 80% of activity)
  - Heterozygote (1:480) = 50; block lasts ~30 minutes
  - Homozygote (1:3200) = 20; block lasts 6-8 hours

Succinylcholine: Adverse Effects

Hyperkalemia
- Can increase K^+ by 0.5-1 mEq/L
- Long list of comorbid contraindications (e.g. hyperkalemic ARF, burn injury, muscular dystrophy, spinal cord injury)

Malignant Hyperthermia
- Trismus (masseter muscle spasm) can be a heralding event

Cardiac Arrhythmias
- Bradycardia - parasympathetic and SA node stimulation; especially in children where sympathetic tone is low.
- Cardiac Arrest - successive doses 2-10 minutes apart can cause bradycardia, junctional rhythm, or arrest; always give 2nd dose with 0.4 mg atropine.

Post-opertive Myalgias
- Fasiculations have been implicated in causing myalgias.
- Prevented with small defasciculating dose of NDMBs.

Increased ICP, IOP, and intragastric pressure

Non-Depolarizing NMBs

- Mechanism of action by competitive inhibition of ACh at the NMJ.
- Two structural classes:
  1. Benzylisoquinoliniums = "-uriums"
     - Atracurium, Cisatracurium, Mivacurium, Doxacurium, d-Tubocurarine
     - More likely to cause histamine release (d-Tubocurarine >> Atracurium = Mivacurium)
  2. Aminosteroids = "-oniums"
     - Pancuronium, Vecuronium, Rocuronium, Pipecuronium
     - No histamine release
     - May exhibit vagolytic effects (Pancuronium >> Rocuronium >> Vecuronium = Pipecuronium)

Non-Depolarizing NMBs

Short-Acting (onset within 90 sec, offset within 20 minutes)
- Mivacurium = 0.2 mg/kg; metabolized by pseudocholinesterase (but slower than SCh)
- Rapacuronium (off the market due to life-threatening bronchospasm)

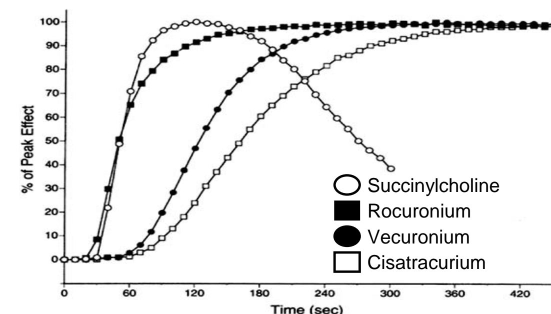
Intermediate-Acting (onset within 3 minutes, offset within 30-45 minutes)
- Rocuronium = 0.6 mg/kg (1 mg/kg for RSI with onset similar to SCh); hepatic > renal elimination
- Vecuronium = 0.1 mg/kg; hepatic > renal elimination
- Cisatracurium = 0.2 mg/kg (0.6 mg/kg for RSI); elimination by Hofmann degradation
- Atracurium

Long-Acting (slow onset, offset ≥60 minutes)
- Pancuronium = 0.1 mg/kg; renal > hepatic elimination
- Pipecuronium, Doxacurium, d-Tubocurarine

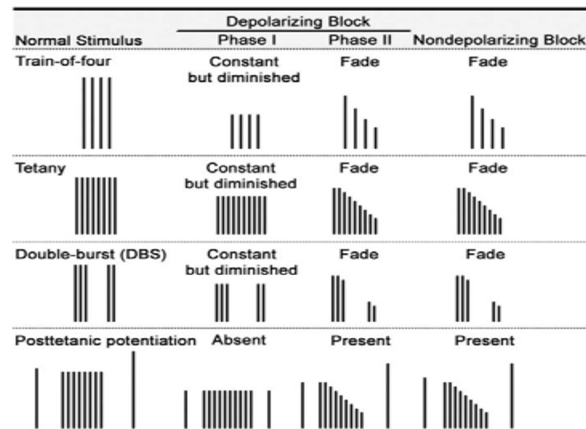
Non-Depolarizing NMBs

- Intubating doses are 2 x ED_{95}
- Precurarization (“defasciculating dose”) with NDMBs reduces the potency and duration of action of SCh.

Time to peak effect for commonly used muscle relaxants



Peripheral Nerve Stimulation



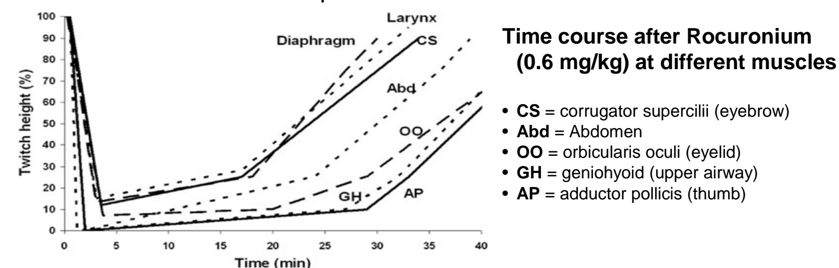
Phase I block is typical for SCh.

Phase II block is typical for NDMBs

SCh can develop a Phase II block at high doses (>6 mg/kg) or with prolonged infusions

Monitoring Neuromuscular Block

- Variability in muscle blockade (most resistant ➔ most sensitive): vocal cords > diaphragm > orbicularis oculi (OO) > abdominal muscles > adductor pollicis (AP) > masseter > pharyngeal muscles > extraocular muscles
- Pick one site to monitor (e.g. AP or eyebrow), but know how different muscles respond relative to that site.



Time course after Rocuronium (0.6 mg/kg) at different muscles

- **CS** = corrugator supercilii (eyebrow)
- **Abd** = Abdomen
- **OO** = orbicularis oculi (eyelid)
- **GH** = geniohyoid (upper airway)
- **AP** = adductor pollicis (thumb)

Monitoring Neuromuscular Block

Onset of Blockade

- The AP poorly predicts intubating conditions because the diaphragm and laryngeal muscles are MORE resistant to blockade.
- The corrugator supercilii (eyebrow) best predicts laryngeal conditions.

Surgical Relaxation

- The AP is adequate, but is more resistant to recovery than the abdominal muscles.
- Surgeons may complain of “tightness” even though you have no AP twitches.

Recovery from Blockade

- The diaphragm and laryngeal muscles recover first.
- The AP recovers last, so if twitches are present, then the diaphragm can be safely reversed.

Anticholinesterases

- Mechanism of action is by inhibiting acetylcholinesterase thereby increasing the amount of ACh in the NMJ.
- Used as “reversal agents” to counteract NDMBs.
  - Neostigmine, Pyridostigmine, and Edrophonium do not cross the BBB.
  - Physostigmine crosses the BBB (can be used to treat central anticholinergic syndrome/atropine toxicity)
- Anticholinesterases cause vagal side effects (e.g. bradycardia, salivation) by increasing ACh activity at parasympathetic muscarinic receptors; always administer with anticholinergics:
  - We typically use Neostigmine 0.07 mg/kg (~2.5-5 mg) with Glycopyrrolate (0.2 mg per 1 mg Neostigmine)
- Other side effects include nausea and bronchospasm.

Reversal of Neuromuscular Blockade

- NDMB activity is terminated by redistribution away from the NMJ and end-organ metabolism.
- Anticholinesterase “reversal agents” speed up redistribution by increasing ACh levels in the NMJ.
- Assess adequacy for reversal with nerve stimulation:
  - TOF ratio = amplitude of 4th twitch divided by 1st twitch
  - When TOF ratio is 0.7, the single twitch height appears normal, but as many as 70% of receptors are still blocked!
  - Patients can be reversed when ≥1 out of 4 twitches is present.
- The gold standard for assessing adequacy of reversal for extubation is 5 seconds of sustained tetany (no fade); other measures include TOF ratio = 0.9 (imperceptible to the eye) or 5 seconds of sustained head lift.

Pearls

- Use Rocuronium for RSI in situations where SCh is contraindicated.
- Consider using Cisatracurium in renal and liver patients (Hofmann degradation).
- Atracurium yields the metabolite “laudanosine”, which can cause CNS stimulation/seizures (but only at high, nonclinical doses)
- Pancuronium is the most renally excreted; causes ↑HR, BP, and CO.
- It is important to pair anticholinesterases and anticholinergics based on speeds of onset:
  - Edrophonium (rapid) w/ Atropine
  - Neostigmine (intermediate) w/ Glycopyrrolate
  - Pyridostigmine (slow) w/ Glycopyrrolate

Pearls

- Diseases more RESISTANT to NDMBs:
  - Guillen-Barré (AChR upregulation)
  - Burns (more extrajunctional nAChR)
  - Spinal cord injury
  - CVA
  - Prolonged immobility
  - Mutliple sclerosis
- Diseases more SENSITIVE to NDMBs:
  - Myesthenia gravis (fewer AChR)
  - Lambert-Eaton Syndrome (less ACh release)
- Factors ENHANCING block by NDMBs:
  - Volatile anesthetics, aminoglycosides, Mg, IV local anesthetics, CCBs, Lasix, Dantrolene, Lithium, anticonvulsants, SCh, hypokalemia, hypothermia

References

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