



# NEUROMUSCULAR BLOCKING DRUGS

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# OBJECTIVES

- History of neuromuscular blockade
- Basic physiology of neuromuscular junction
- Pharmacology of neuromuscular blocking drugs
- Principles of monitoring
- Complications of neuromuscular blockade



# HISTORY OF NEUROMUSCULAR BLOCKADE

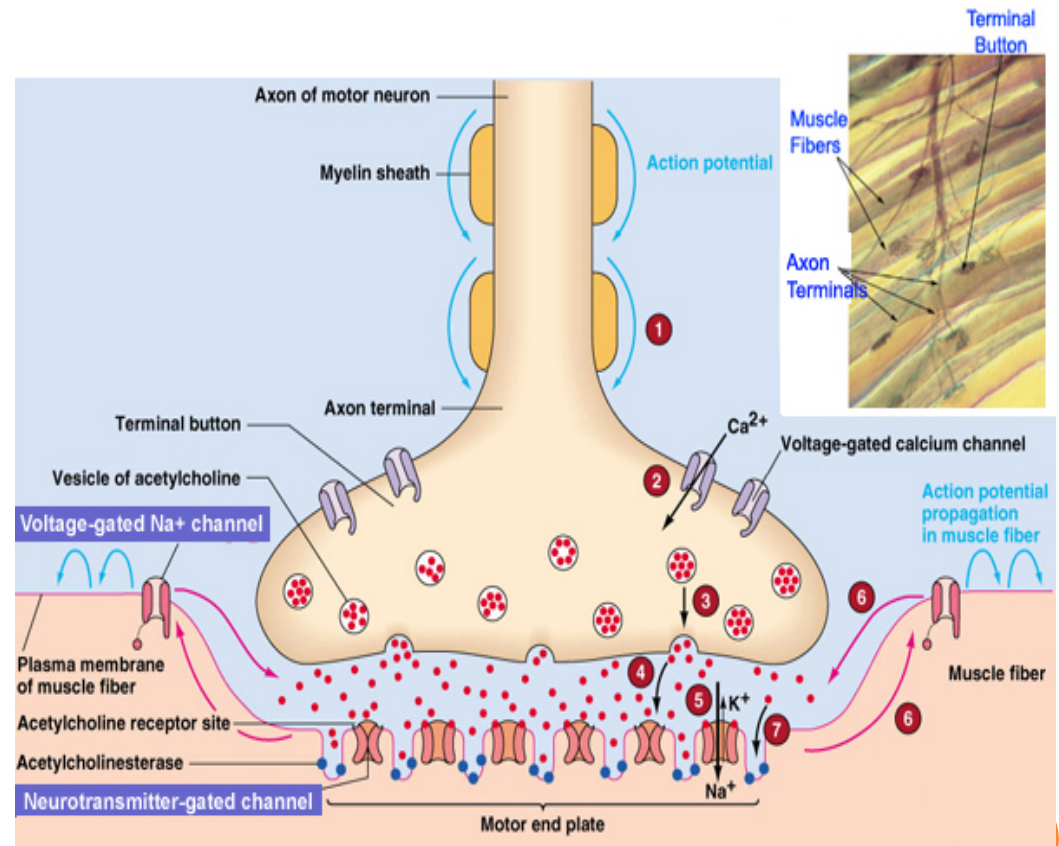
- First known use was by South American natives shot poison arrows loaded with curare to paralyze prey. (Sir Walter Raleigh 1596)
- Experiment with curare on animals in 1800 - can keep animals alive with artificial respiratory support
- 1914 - Henry Dale described actions of acetylcholine. Later showed that curare could block NMJ transmission.
- Curare can be ingested without GI absorption, thus safe for South American natives to eat prey.



# NEUROMUSCULAR JUNCTION

- Synapse between an axon terminal and motor end plate
- highly excitable region of the muscle fiber that initiates action potential

The Neuromuscular Junction



# EXCITATION-CONTRACTION COUPLING

- Steps involved in excitation-contraction coupling:
  - 1. Stimulus (impulse) through prejunctional axon causes an influx of Ca ions
  - 2. Ca influx causes release of ACh, which ultimately bind to post junctional nicotinic cholinergic receptors
  - 3. Causes a change in K and Na permeability (Na moves intracellular, K moves extracellular) that decreases the transmembrane potential (-90 --> -45 mV)
  - 4. When the potential reaches the threshold, the action potential is propagated throughout the muscle fiber.



# WHAT ARE NEUROMUSCULAR BLOCKING DRUGS (NMBDs)?

- Drugs that block the transmission of nerve impulses at the NMJ → causes paralysis
- Uses:
  - facilitate endotracheal intubation and/or mechanical ventilation
  - provide optimal surgical conditions



# INFORMATION ON NMDBs

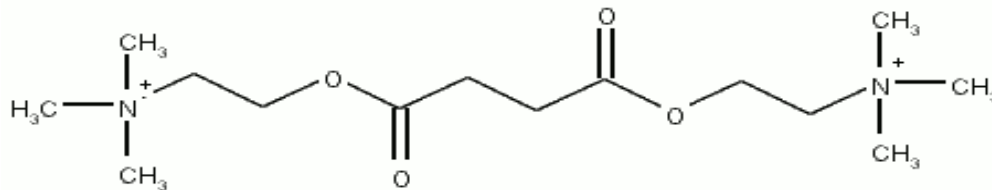
- Curare developed first, but newer agents later followed.
- Classified using various properties:
  - Mechanism of action
  - Duration of action
  - Pharmacological structure
- The ideal relaxant:
  - Fast onset
  - Non-cumulative
  - Easily eliminated
  - Reversible
  - No side effects



# DEPOLARIZING AGENTS

## ○ Succinylcholine

- the only depolarizing agent clinically used today
- composed of two ACh molecules linked together
  - ACh hits receptors, causing depolarization and subsequent action potential
  - Paralysis occurs due to depolarized membrane potential and inactivated sodium channels
- rapid onset (30-60 sec) and short duration (5-10 min)
- Plasma cholinesterase (synthesized in liver) hydrolyzes SCh and ACh quickly (only a fraction of dose reaches NMJ)



# SUCCINYLCHOLINE

## ○ Pros:

- Fast acting
- Short duration

## ○ Cons:

- MH trigger
- Acute hyperkalemia (burns, paraplegia, children)
- Myalgia upon emergence
- Cardiac dysrhythmias (bradycardia/tachycardia, arrest, junctional rhythm)
- Increased intraocular and intragastric pressure



# NON-DEPOLARIZING NMBDs

- Mechanism: competitive inhibition with ACh of post-synaptic receptors, preventing depolarization
- Due to their quaternary ammonium groups
  - highly ionized
  - water soluble
  - do not cross BBB or gastric epithelium
- Benzylisoquinolones vs. Aminosteroids
- Long vs. intermediate vs. short acting agents



# LONG-ACTING NON-DEPOLARIZERS

## ○ Pancuronium

- bisquaternary aminosteroid
- 3-5 min onset of action, 60-90 min duration
- 80% eliminated unchanged in urine → renal failure leads to prolonged action
- Can cause 10-15% increase in HR, MAP, and CO
  - via selective blockade of cardiac muscarinic receptors (atropine-like)
- Caution: may increase myocardial oxygen demand, thus leading to myocardial ischemia if CAD



# INTERMEDIATE-ACTING AGENTS

## ○ Benzylisoquinolones

### ● Atracurium

- Onset of 3-5 min; duration of action 20-30 min.
- Metabolized by Hofmann elimination and ester hydrolysis (renal or hepatic impairment do not affect metabolism)
- Rapid administration may cause histamine release (tachycardia, hypotension)
- Produces laudanosine, which causes nervous system stimulation.

### ● Cisatracurium

- Isolated stereoisomer of atracurium
- Metabolized only by Hofmann elimination
- Unlike atracurium, it does not cause histamine release.



# INTERMEDIATE ACTING AGENTS (CONT.)

## ○ Aminosteroids

### • Vecuronium

- Similar onset time and duration as atracurium
- Undergoes hepatic and renal excretion
- Virtually no cardiovascular effects

### • Rocuronium

- Time of onset depends on administered dose as large doses may act as quickly as succinylcholine.
- Excreted via renal and biliary processes
- No histamine production



**Table 1. Dosing Guidelines and Pharmacodynamic Parameters of NMB Agents\***

Class	Drug (Trade Name, Manufacturer)	Intubation Dose, <sup>†</sup> mg/kg	Onset, <sup>‡</sup> min	Duration, <sup>§</sup> min	Long Surgical Procedures	
					Repeat Bolus, <sup>†</sup> mg/kg	Average Infusion Rate <sup>†,§</sup> (range)
Ultra-short-acting	Succinylcholine (various)	0.6 (0.3-1.1)	1	4-6	0.04-0.07	2.5-4.3 mg/min (0.5-10)
Intermediate-acting	Atracurium (various)	0.4-0.5	3-5	20-35	0.08-0.1	5-9 mcg/kg/min (2-15)
	Cisatracurium (Nimbex, GlaxoWellcome)	0.15-0.2	1.5-2	55-61	0.03	1-2 mcg/kg/min (1-3)
	Rocuronium (Zemuron, Organon)	0.6 (0.45-1.2)	1-3	22-67	0.1-0.2	10-12 mcg/kg/min (4-16)
	Vecuronium (various)	0.08-0.1 (up to 0.28)	2.5-3	25-30	0.01-0.015	1 mcg/kg/min (0.8-1.2)
Long-acting	Pancuronium (various)	0.06-0.1	2-4	60-100	0.01-0.06	—

\* NMB agents should always be used in combination with sedative and/or anesthetic agents.

† Dosing information pertains only to adults and may vary based on the use of co-induction agents.

‡ The onset of time to maximum block or time to good/excellent intubation conditions is dose dependent.

§ Clinically effective duration of action.

|| Infusion doses reflect initiation after early evidence of spontaneous recovery from the initial bolus dose.

Based on prescribing information/manufacturer's data and reference 4.

# MONITORING NEUROMUSCULAR BLOCKADE

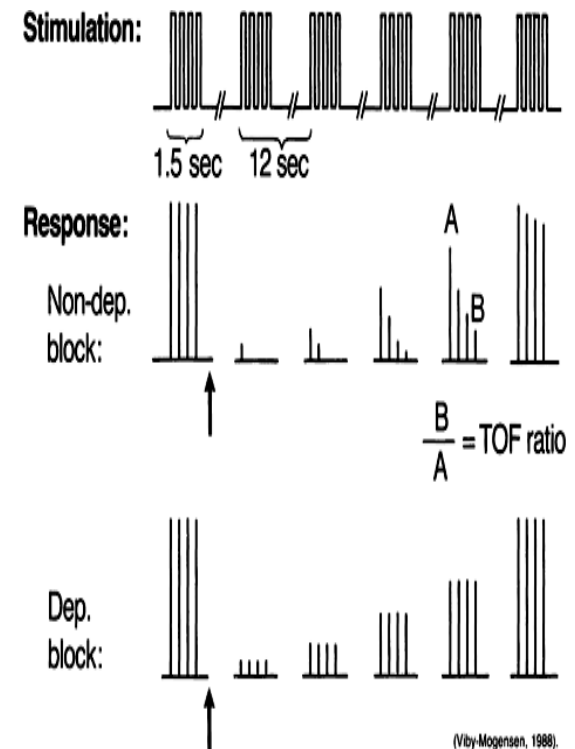
- Most effective method of measuring degree of neuromuscular blockade is electrical stimulation.
  - Device
    - delivers an electrical stimulus
    - facial or ulnar nerve.
  - Diaphragm most resistant
  - Peripheral muscles least resistant
  - Response to stimulus varies depending on the depth of blockade.



# MONITORING: ELECTRICAL STIMULI

## ○ Train-of-four (TOF)

- 4 electrical stimulations delivered over 2 sec and twitch response is evaluated.
- ACh should be depleted with successive stimulations
- With succinylcholine, all four twitches should have same amplitude.
- TOF ratio is determined using the height of the fourth-to-first twitch.
- Decreasing twitch response is seen with non-depolarizers (fade).



# TRAIN-OF-FOUR

Number of Twitches	Approx. % of receptors blocked	Significance
4	0-75	Pt able to move, but may need reversal
3	75	May need additional relaxation for procedure
2	80	Minimum relaxation for intra-abdominal procedures
1	90	Suitable for short procedures or mechanical ventilation
0	100	Ideal intubating conditions



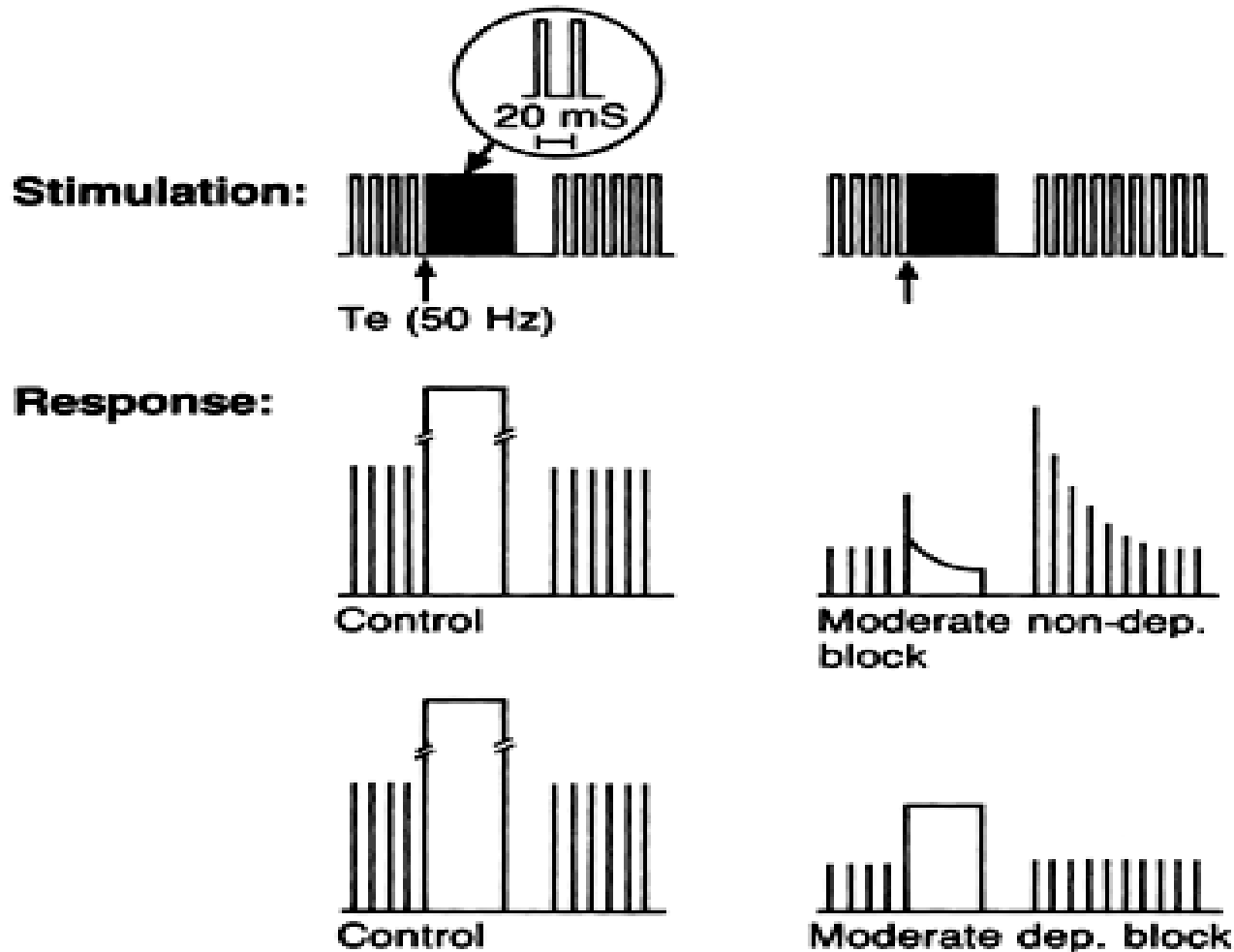
# ELECTRICAL STIMULI













## ○ Tetany

- Continuous electrical stimulus for at least 5 sec that releases ACh at the NMJ.
- Fade may be seen with non-depolarizers, but not depolarizing agents.
- Sustained tetany is seen when the TOF ratio is greater than 0.7
- Post-tetanic facilitation – increase in ACh stores such that subsequent stimuli produce enhanced responses.



# TETANY



No Drug	Nondepolarizing Block	Depolarizing Block	
		Phase I	Phase II
Train-of-four  TOF-R = 1.0	Fade  TOF-R = 0.4	Constant but diminished  TOF-R = 1.0	Fade  TOF-R = 0.4
Double burst 	Fade 	No fade 	Fade 
Posttetanic potentiation  * PTC = > 6	Present  PTC = 3 *	Absent  *	Present  PTC = 3 *

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: <http://www.accessmedicine.com>

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# ANTAGONISM OF BLOCKADE

- Pharmacological antagonism of neuromuscular blockade with an anticholinesterase
  - ie. Neostigmine, pyridostigmine, edrophonium
  - Inhibits acetylcholinesterase activity, thus allowing ACh to accumulate at nicotinic (NMJ) and muscarinic receptors.
    - May lead to bradycardia, so co-administration of an anticholinergic (ie. atropine, glycopyrrolate) is routine
  - Large molecular structure prevents CNS infiltration and any possible neurological effects



# CLINICAL CONSIDERATIONS OF REVERSAL

- Given only after the patient demonstrates at least one twitch during TOF
- Beware of recurarization or prolonged block with pancuronium despite adequate reversal dose given
- Factors that may prolong neuromuscular blockade:
  - Certain antibiotics (aminoglycosides, clindamycin, polymyxins)
  - Inhalational and local anesthetics
  - Electrolytes (Lithium, Magnesium)
  - Physiological state (acidosis, alkalosis, hypothermia)



# WHAT IS ADEQUATE REVERSAL?

- What are some indicators to look for?
  - TOF > 0.7
  - Sustained head lift > 5 sec
  - Grip strength
  - Ability to follow commands
  - Tidal volume > 5cc/kg



# QUESTIONING THE REVERSAL

- Things to consider:
  - Adequate time given for anticholinesterase to take effect?
  - Adequate dose given?
  - Temperature?
  - Electrolytes?
  - Coexisting renal/hepatic disease?



# SCENARIO

- A 63 year old gentleman with a history of DM, CAD, and chronic renal insufficiency undergoes a successful open radical cystectomy for bladder CA. He is brought to the PACU intubated because of delayed emergence due to the inability to spontaneously ventilate. What are some possible etiologies of his status?



# DIFFERENTIAL DIAGNOSIS

- Prolonged neuromuscular blockade
- Check vitals, oxygenation status
- Medications
  - Opioids/Benzodiazapines
- Hypoglycemia
- Electrolyte abnormalities
- Cerebral vascular accident
- Seizure



# TAKE HOME CLINICAL APPLICATIONS

- As perianesthesia care givers:
  - Know basics about various paralytic agents
  - Understand principles of monitoring neuromuscular blockade
  - Be able to assess adequacy of reversal
  - Be aware of factors that influence block
  - Know differential diagnosis of prolonged block

