

Joseph F. Answine, MD

Staff Anesthesiologist
Pinnacle Health Hospitals

Harrisburg, PA

Clinical Associate Professor of
Anesthesiology

Pennsylvania State University
Hospital

Reversal of Neuromuscular Blockade

Definitions

- **ED₉₅** - dose required to produce 95% suppression of the first twitch response.
- **2xED₉₅** – the ED₉₅ multiplied by 2 / commonly used as the standard intubating dose for a NMBA.
- **T1** and **T4** – first and fourth twitch heights (usually given as a % of the original twitch height).
- **Onset Time** – end of injection of the NMBA to 95% T1 suppression.
- **Recovery Time** – time from induction to 25% recovery of T1 (NMBAs are readily reversed with acetylcholinesterase inhibitors at this point).
- **Recovery Index** – time from 25% to 75% T1.

Pharmacokinetics and Pharmacodynamics

- What is **Pharmacokinetics**?
- The process by which a drug is absorbed, distributed, metabolized and eliminated by the body.
- What is **Pharmacodynamics**?
- The study of the action or effects of a drug on living organisms. Or, it is the study of the biochemical and physiological effects of drugs. For **example**; rocuronium reversibly binds to the post synaptic endplate, thereby, inhibiting the binding of acetylcholine.

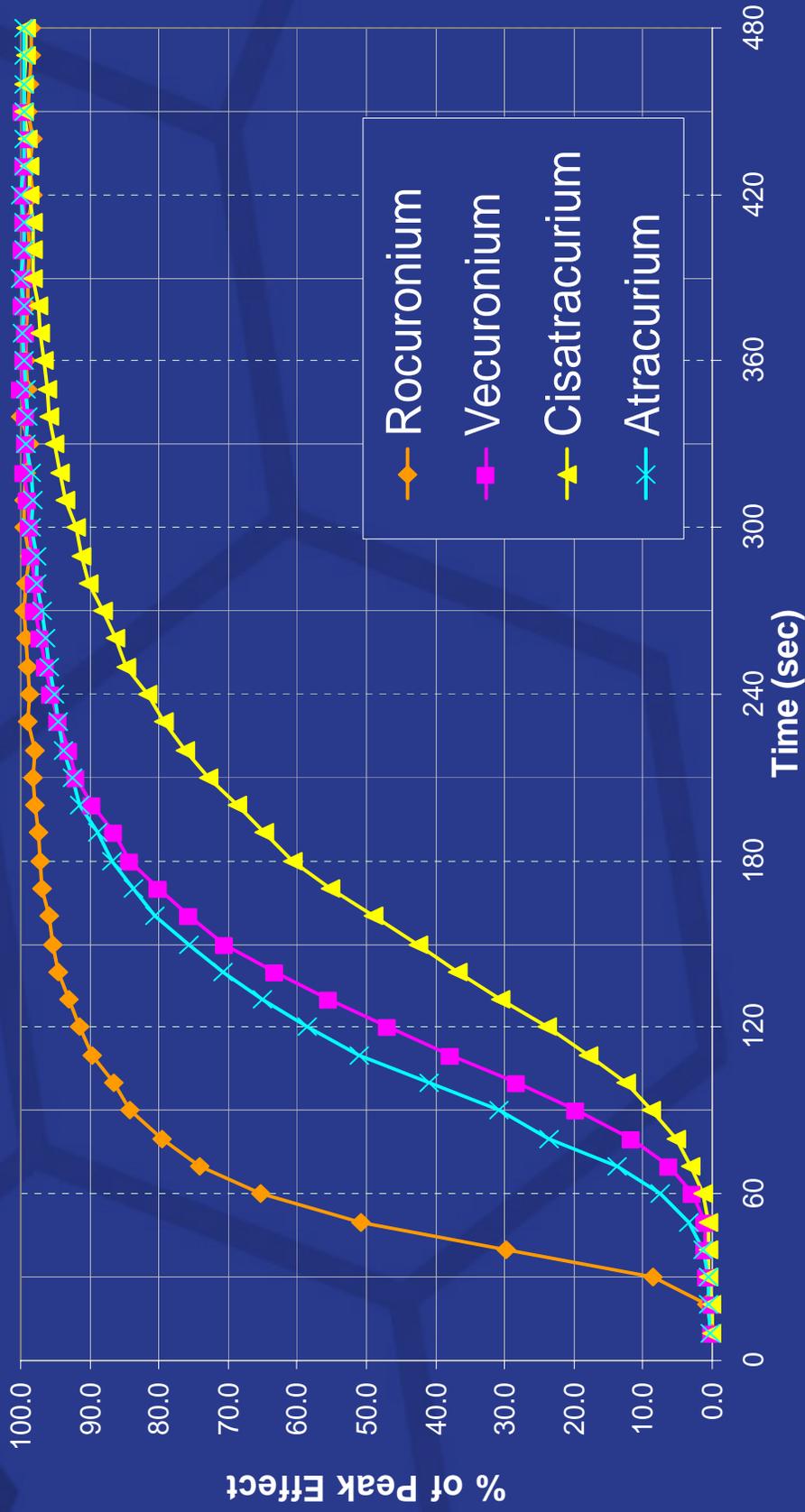
Structural Classes of Nondepolarizing Relaxants

- **Steroids:** rocuronium bromide, vecuronium bromide, pancuronium bromide, pipecuronium bromide.
- **Benzylisoquinoliniums:** atracurium besylate, mivacurium chloride, doxacurium chloride, cisatracurium besylate
- **Isoquinolones:** curare, metocurine

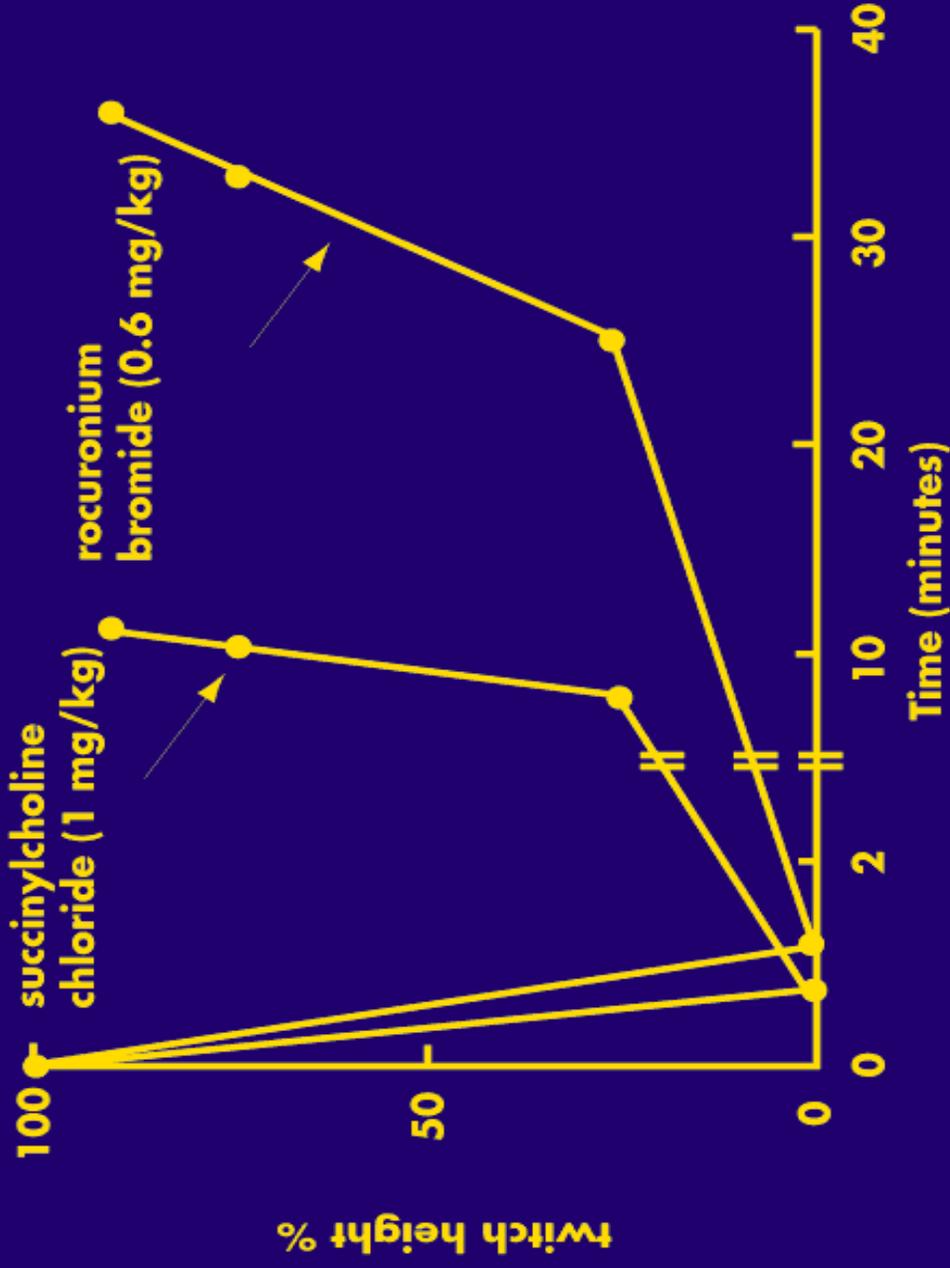
Onset of paralysis is affected by:

- Dose (relative to ED_{95})
- Potency (number of molecules)
- K_{E0} (plasma equilibrium constant - chemistry/blood flow) — determined by factors that modify access to the neuromuscular junction such as cardiac output, distance of the muscle from the heart, and muscle blood flow (pharmacokinetic variables).

Onset Time of Nondepolarizing NMBA's



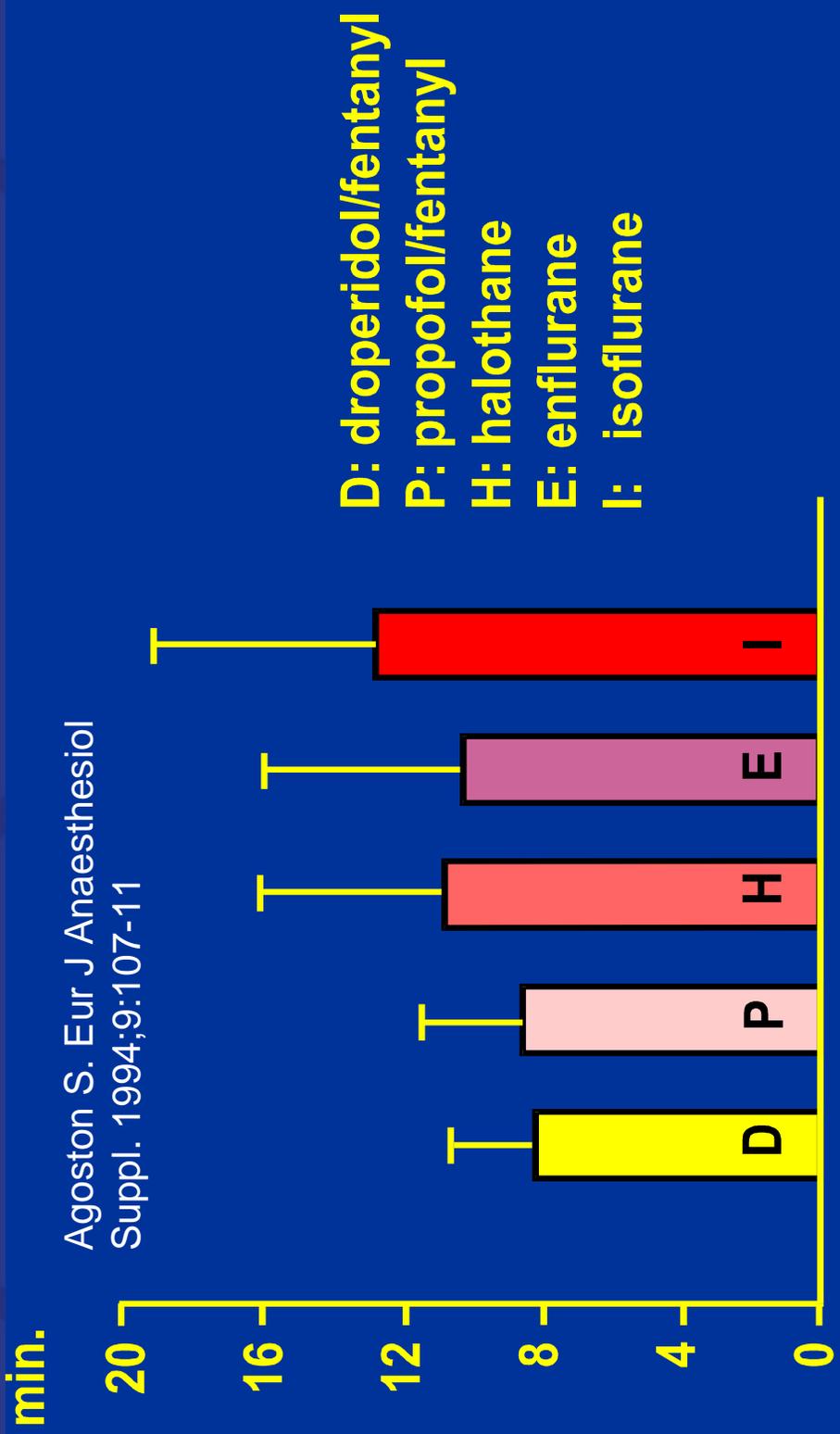
Onset* and recovery from block



Adapted from: Puhlinger FK, et al Anesth Analg 75:37-40, 1992

*Onset: time from end of injection to depression of T1 to 95 % block

Effects of anaesthetics on clinical duration of rocuronium bromide 0.3 mg/kg



Neuromuscular Blocking Agents: Drug Interactions (anesthetics)

- Requirements for NMBAs will be reduced by 10% to 25% when using potent inhalational agents such as isoflurane.
- There appears to be no change in requirements for NMBAs when using propofol or other IV anesthetics.

Potentialiation of Non Depolarizing Agents

- Acid-base and electrolyte disturbances
 - a. respiratory acidosis,
 - b. magnesium,
 - c. calcium,
 - d. K+
- Drugs:
 - a. Anesthetic inhalation agents
 - b. Antibiotics
- Hypothermia
- **All the above are commonly present at the end of an anesthetic and in the recovery room.**

Key Points: Elderly and Neuromuscular Blockers

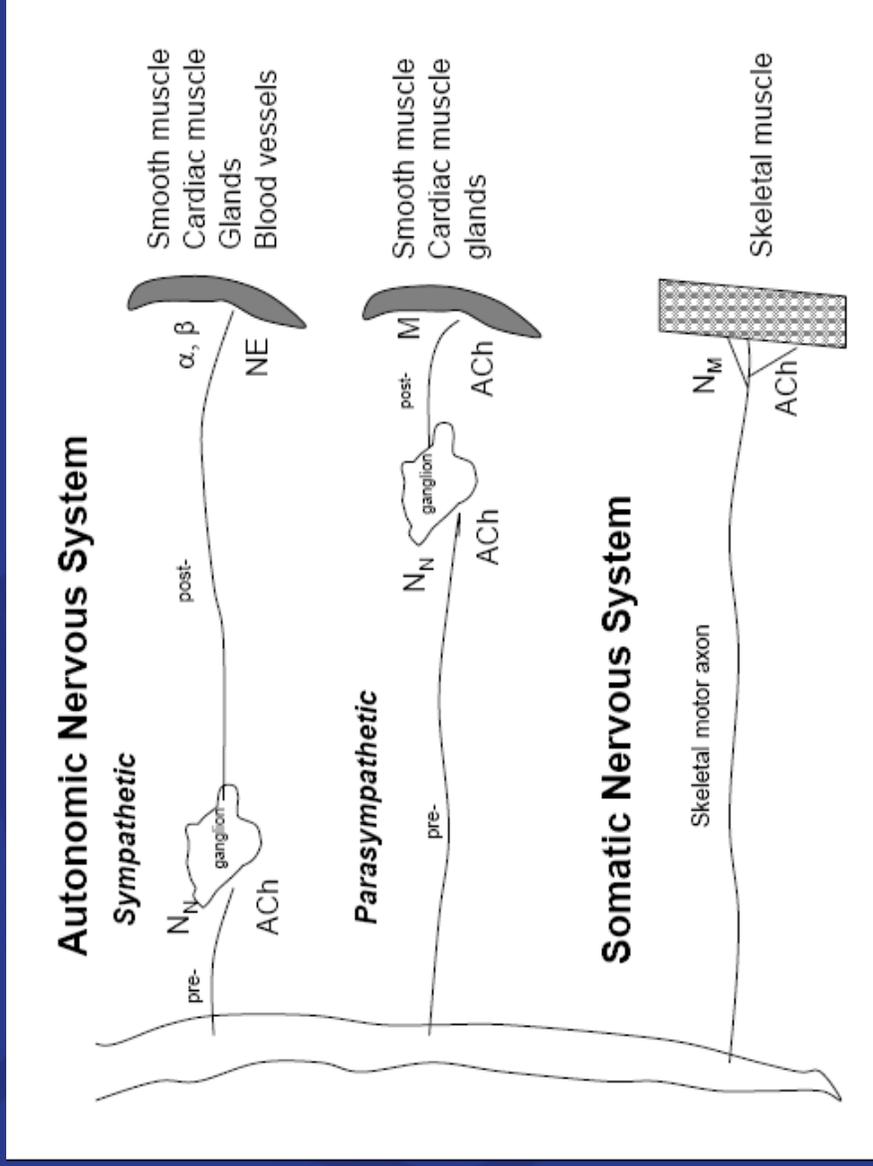
- There is a slightly slower onset of neuromuscular blockade (likely secondary to slower delivery of rocuronium to the neuromuscular endplate (Keo)).
- There is a slower offset secondary to a decreased metabolism of rocuronium (decreased organ mass and overall function with normal aging).
- Variability is more likely as we get older because disease processes affecting the pharmacokinetics and pharmacodynamics of NMBAs are likely to be present.

Key Points: Children and Neuromuscular Blockers

- There is a faster onset in neonates but a delayed offset.
- This is likely secondary to an immature neuromuscular endplate leading to a quicker onset, and an immature liver and kidneys leading to slower metabolism and a delayed offset.
- In children (1 to 5 years), the onset time and the duration approach young adults as organ systems complete their development.

Some Physiology (of the Neuromuscular junction)

What are we talking about?



The Neuromuscular Junction (NMJ)

- The NMJ is a chemical synapse with a **neuronal pre-synaptic terminal** where Ach is released, and a **post-synaptic membrane** where the cholinergic receptors reside.
- Ach is synthesized in the pre-synaptic terminal by **choline-O-acetyl transferase** from choline and acetate.
- Ach is stored in the cytoplasm of the pre-synaptic terminal and transported into vesicles which are moved into position for release. Each vesicle contains approximately 5 x 10 to the 3rd molecules of Ach.
- The vesicles are aligned exactly opposite the convolutions (where nicotinic receptors are concentrated on the post-junctional muscle membrane).
- Acetylcholinesterase (AChE) is present in the area of the cholinergic receptor to deactivate the Ach.

The Neuromuscular Junction

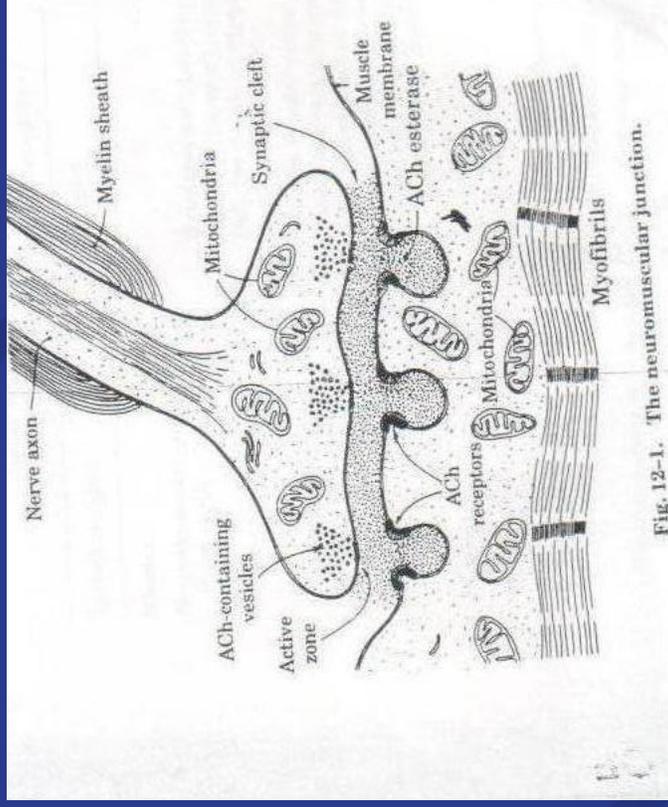
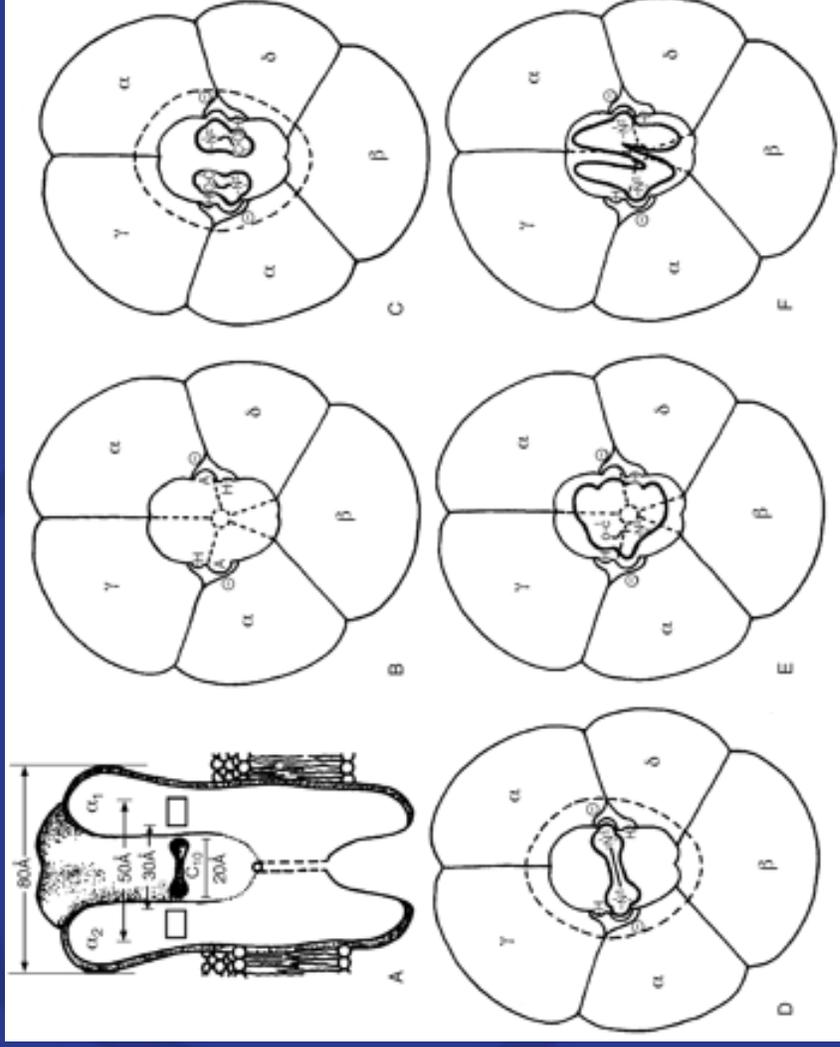


Fig. 12-1. The neuromuscular junction.

Structure of the Acetylcholine Receptor

- It is a pentameric site.
- The five subunits are arranged in a rosette around a Na-K ionic channel.
- Each receptor has two Ach receptive sites.
- Two Ach molecules must bind to the receptor to open the channel.
- The potency of a NMBA depends on how well the agent fits into the receptor (e. g. cis-atracurium [0.1-0.2 mg/kg] is more potent than rocuronium [0.6 mg/kg], therefore, it must be a better “fit” with the receptor).

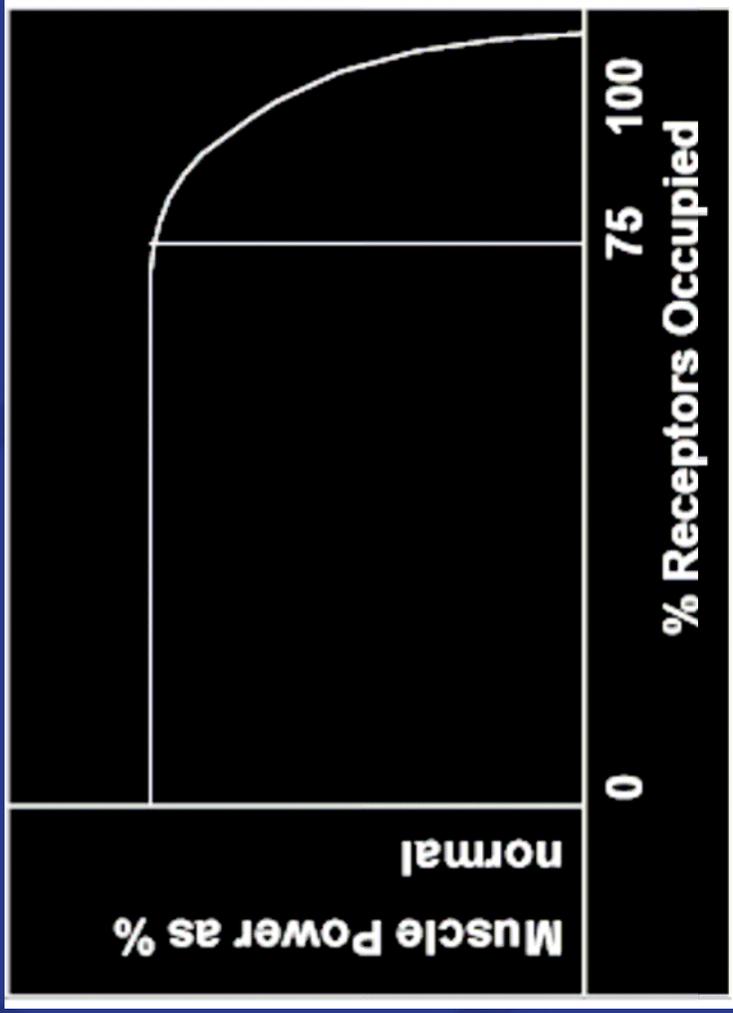
The Acetylcholine Receptor



Physiology of the Neuromuscular Junction

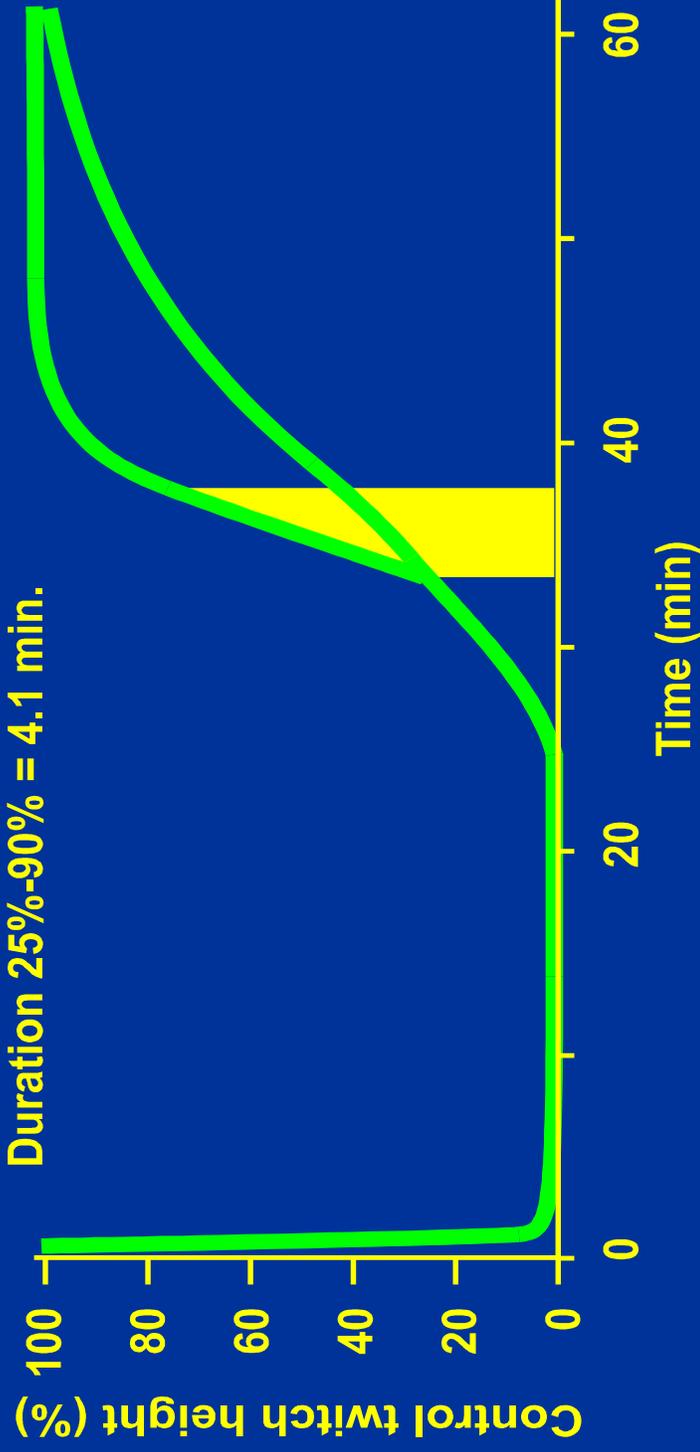
- An action potential results in release of Ach at the pre-synaptic terminal.
- ACh interacts with (neuromuscular) NM receptors at the end-plate.
- Depolarization of the end-plate membrane results.
- Muscle contraction is initiated.
- ACh is inactivated by acetylcholinesterase (AChE).
- Mechanisms of Neuromuscular Blockade
 - Receptor blockade (non-depolarizing agents)
 - Depolarization of the end-plate (depolarizing agents)
- The effect of neuromuscular blockade is skeletal muscle paralysis.

The post-synaptic terminal: a redundant system



**So, how do we reverse
neuromuscular blockade?**

Rocuronium bromide 0.6 mg/kg reversal of block



Adapted from Van den Broek et al. Eur J Anaesth. 11 (9) pp 128-132, 1994

There are two components involved with the reversal of neuromuscular blockade; removal of the NMBA from the neuromuscular junction by redistribution and metabolism, and chemical reversal with AChE inhibitors.

Acetylcholinesterase (AChE) Inhibitors

- Neostigmine (prostigmin), edrophonium (tensilon), pyridostigmine (mestinon) are most commonly used as reversal agents.
- Their primary mode of action is the inhibition of AChE (therefore allowing the neurotransmitter acetylcholine to be present at the neuromuscular junction longer).
- Onset of action: Edrophonium (1-2 min), Neostigmine (7-11 min), pyridostigmine (16 min)
- The reason for the rapid onset of edrophonium as compared to the other two is not clear. All three inhibit AChE as soon as they bind with the enzyme.
- Neostigmine and pyridostigmine are hydrolyzed by AChE. The enzyme is carbamylated in the process reducing its ability to hydrolyze acetylcholine.
- Edrophonium is not broken down by AChE. The interaction is competitive and reversible.
- The actual duration of action of all three is 1-2 hours. We never see it clinically in the OR because the neuromuscular blocking agents are usually metabolized faster.

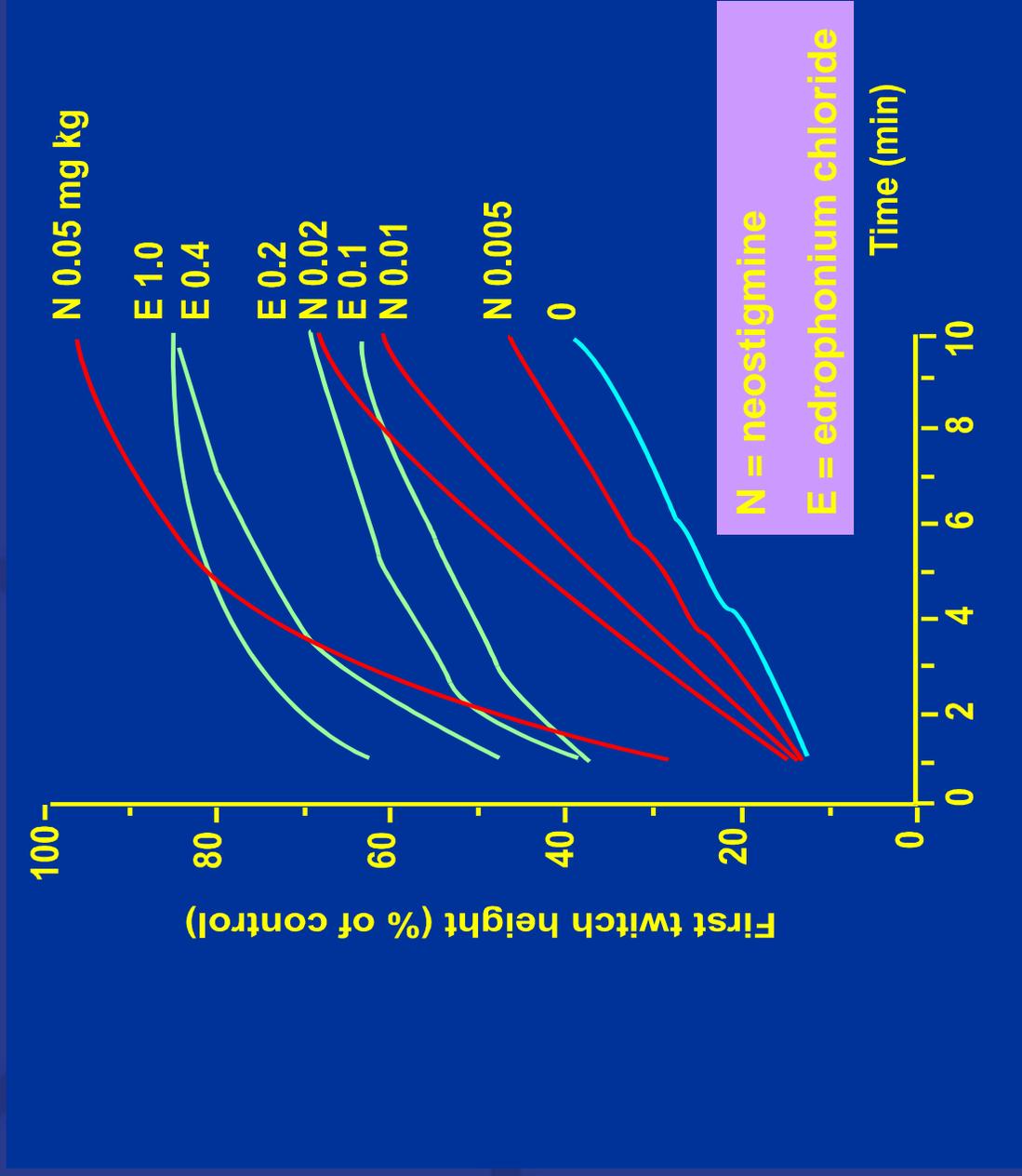
Dosing of AchE Inhibitors

- Edrophonium – 0.5 – 1.0 mg/kg
(Max. effect 1 minute)
- Neostigmine - 0.03 – 0.06 mg/kg
(Max. effect 7 minutes)
- Pyridostigmine – 0.25 mg/kg
(Max. effect 10-13 minutes)
- The duration of action for all three agents is about 1-2 hours.

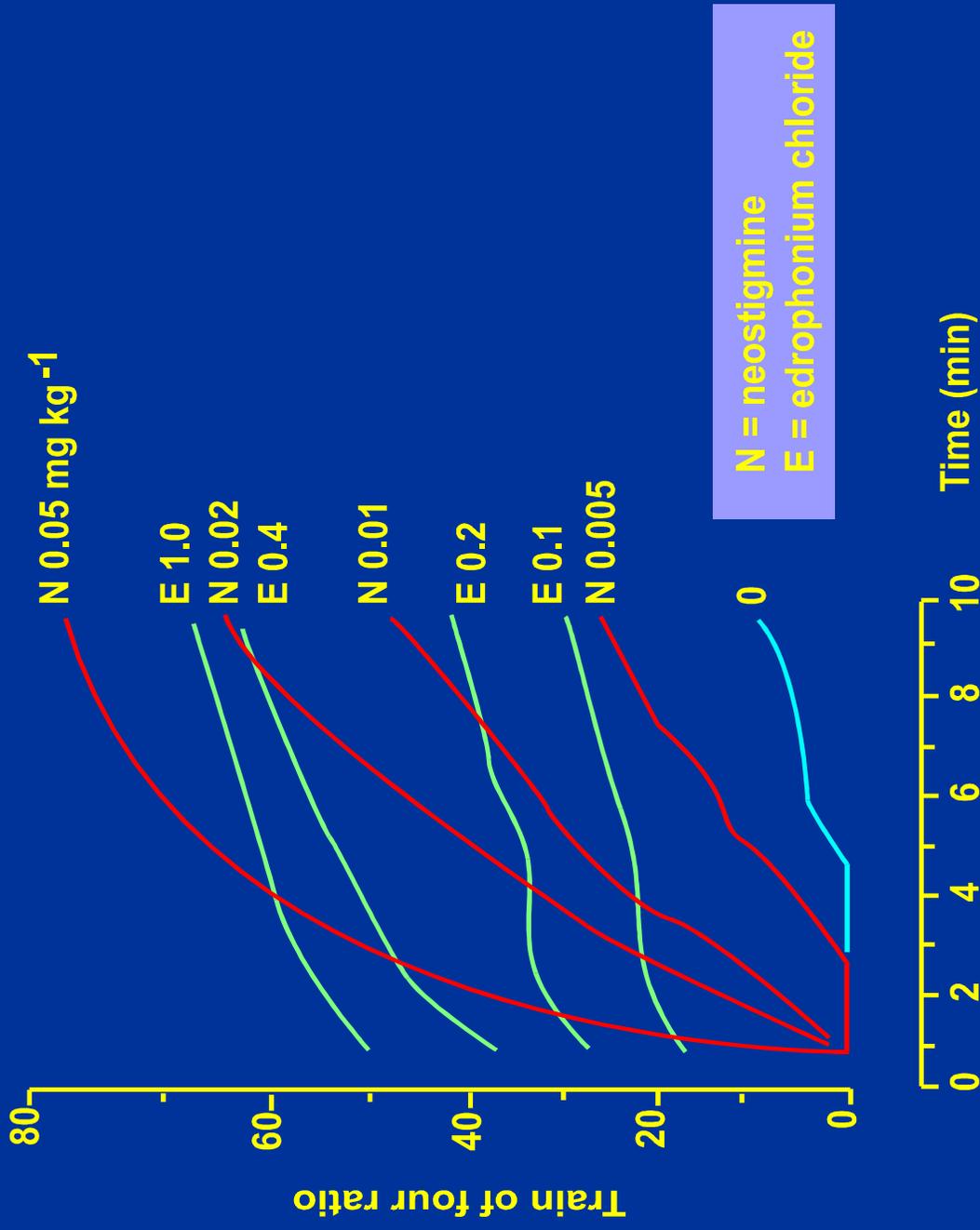
Anticholinergic Drugs (dosing) with 0.5 to 1.0 mg/kg Edrophonium or 50 to 70 microgram/kg Neostigmine

- **Atropine** – 10 microgram/kg
- **Glycopyrrolate** – 5 to 10 microgram/kg
(Usually given one minute before Edrophonium)

Antagonism of rocuronium bromide (0.6 mg/kg)



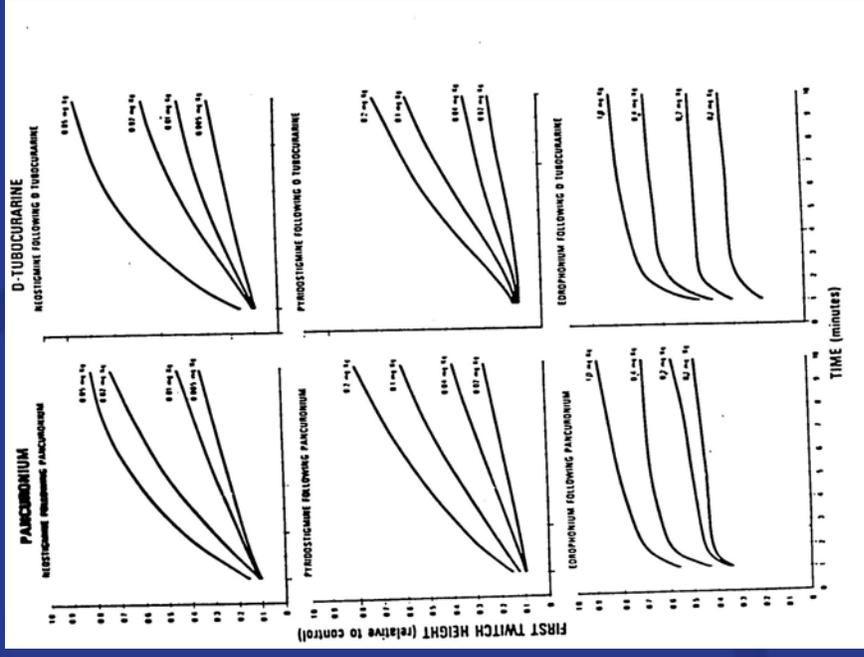
Antagonism of rocuronium bromide (0.6 mg/kg)



Is there a different mechanism of action between AchE inhibitors? What do we know?

- Edrophonium and neostigmine are not equally effective especially with more intense levels of blockade.
- The onset of edrophonium is faster than the others even though the inhibition of AchE is felt to occur immediately upon its binding with all of the agents.
- Edrophonium assisted antagonism of AchE is known to have a “flatter” dose-response curve than that of neostigmine.

Dose / Response Curves (AChE Inhibitors)



Acetylcholinesterase Inhibitors: Possible Alternative Mechanisms of Action

- Presynaptic effects (either by directly binding to, or by having an increased amount of Ach present at the presynaptic receptor)
- Direct action (binding) at the postsynaptic acetylcholine receptor

Ceiling Effect of Acetylcholinesterase Inhibitors

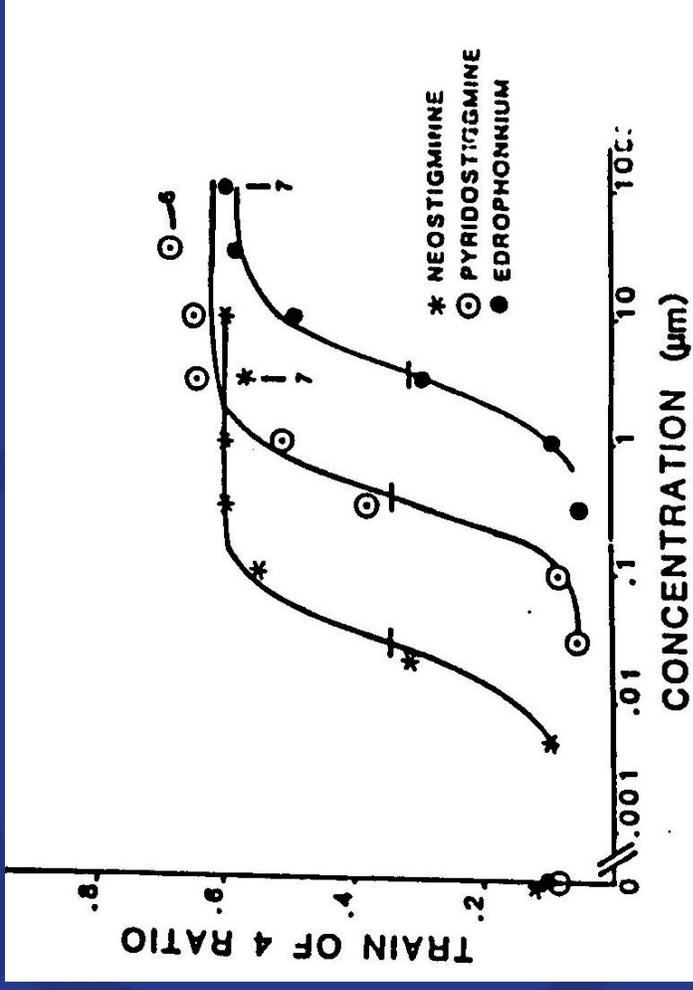


FIG. 5. Ceiling effect of anticholinesterases. Relationship between concentrations of neostigmine, edrophonium, and pyridostigmine: train-of-four ratio after reversal of 95% block in a phrenic nerve-diaphragm preparation.¹⁰¹

Side Effects of AchE Inhibitors

- cardiac arrhythmias (especially bradycardia)
- bronchoconstriction
- increased salivation
- ? increased incidence of nausea and vomiting (many studies disagree with this hypothesis)
- weakness in certain patient populations

Drawbacks to Acetylcholinesterase

Inhibitors

- They are “indirect” acting agonists for Ach.
- You cannot effectively reverse profound ($T_1 < 10\%$ baseline) blockade of the neuromuscular junction (the time to achieving extubation criteria with or without reversal using an AchE inhibitor from a profound block is the same). Multiple or excessive doses of AchE inhibitors may increase the degree of residual blockade.
- The effect is not selective, therefore, there are a few side effects with their use such as; increased salivation, bradycardia, tearing, miosis and bronchoconstriction.
- They must be given with other drugs such as atropine and glycopyrrolate to antagonize the muscarinic effects of Ach.
- AchE inhibitors are not true “rescue” reversal agents for the “cannot ventilate / cannot intubate” patient.

The Time to Adequate Reversal with AchE Inhibitors Depends on the Specific NMBA.

- Intermediate Acting Agents (e. g. rocuronium, vecuronium) - 7 – 12 minutes
- Long Acting Agents (e. g. pancuronium, curare) – 20 – 40 minutes

How do we assess adequacy of reversal of neuromuscular blockade?

Twitch Monitor

- Train Of Four (compare the 4th twitch to the 1st twitch)
- You want the ratio of the fourth/first twitch to be > 0.7 (actually current thought is that a ratio of > 0.9 is needed).
- Sustained Tetanus
- Double Burst Stimulation
- TOF is usually assessed by visual inspection and not using quantitative measures (acceleromyography and mechanomyography).
- Sustained Tetanus and Double Burst Stimulation are also very difficult to quantify.

How do we assess adequacy of reversal of neuromuscular blockade?

Other Clinical Indicators

- Head Lift (5 or 10 seconds)
- Leg Lift (in children)
- Hand Grasp
- Negative Inspiratory Force (NIF)
- Head Lift > 10 seconds is best, but sometimes it is hard to get the patient to follow the command to lift his/her head.
- Kopman et. al. (1997) – the tongue depressor test – If a patient can grasp a tongue depressor between his/her teeth and it cannot be pulled out, the TOF is likely > 0.85 and upper airway muscular function is likely intact.

Some History

- Ali et. al. (1970 and 1971) – When 4 stimuli were delivered at 0.5-s intervals, there was a progressive fade of successive responses depending on the extent of curarization. TOF was defined. At values of > 0.7 , no evidence of paralysis was noted.
- Engbaek et. al. (1989) – This study described the technique of “double burst stimulation” in response to complaints of difficulties in the clinical assessment of TOF fade.
- Brull et. al. (1990) – They noted a close linear relationship between TOF and double burst stimulation.

How do we assess TOF fade?

- Mechanomyogram (MMG), EMG and accelerography can be used, however the equipment can be expensive and difficult to use.
- Most of us rely on the subjective assessment of the TOF.
- Viby-Mogensen et. al. (1985) – TOF fade went frequently undetected (even values as low as about 0.4).
- Dupuis et. al. (1990) – Sustained tetanus was noted at TOF ratios of < 0.5 .
- Drenck et. al. (1989) – The ability to identify fade increased to a level of 0.6 with double burst stimulation (still not > 0.7).
- **Remember that many believe that a TOF ratio $> 70\%$ is still inadequate ($> 90\%$ is needed).**

Classic Teaching States that a TOF ratio of 0.7 (Ali et. al. 1981) is an Appropriate Level of Reversal for Extubation.

What is an appropriate TOF ratio for adequate reversal (what some studies have noted)?

- TOF ratio of 0.63 – You may see patients complain of difficulty breathing and swallowing as well as a decreased inspiratory force and peak flow rate.
- TOF ratio of 0.7 to 0.75 – You may see diplopia, decreased grip strength, inability to sit up without assistance, facial weakness and difficulty swallowing and speaking . Also, studies have shown decreased coordination of esophageal musculature and pharyngeal dysfunction leading to a 4 to 5 fold increase in the risk of aspiration (Eriksson et. al. 1997). Pharyngeal function returns to normal with a TOF ratio of 0.9.
- TOF of 0.85 – You may see general discomfort, malaise, ptosis, and blurred vision.
- TOF of 0.9 – You may see significant visual disturbances such as diplopia and difficulty tracking objects.

**Recent studies in Humans Indicate
that the “Bar” for an Acceptable
Level of Recovery of
Neuromuscular Function should
be Raised to a TOF Ratio of
> 0.90.**

Clinical Evaluation

- Dam and Guildmann (1961) – described the “head lift” as a reliable sign of muscle power [didn’t specify the duration]
- Many have demonstrated that a head lift for > 5 seconds is a reliable indicator of adequate reversal of neuromuscular blockade
- Ali et. al. (1971) – no patient with a TOF ratio < 0.4 could lift his/her head off of the bed
- Hutton et. al. (1976) – 5 second head lift however does not guarantee that voluntary function has returned to normal or that they are comfortable.
- Many patients will not follow the command to lift their head, or they will not do it secondary to pain from the surgical site.
- Using “hand grip” is much less reliable.
- In infants, a leg lift correlated with a “NIF” (negative inspiratory force) of -58 cm H₂O to -71 cm H₂O therefore it is a reasonable indicator of return of neuromuscular function in this population.

Negative Inspiratory Force (NIF)

- Bendixen et. al. – They suggested that the maximum negative pressure (negative inspiratory force generated against a closed airway) could be a measurement of ventilatory reserve.
- Wescott et. al. (1962) – suggested that as little as -20 cm H₂O indicated sufficient ventilatory reserve.
- -25 cm H₂O to -30 cm H₂O became an acceptable goal for determining recovery of neuromuscular function.
- However, it has been shown that a head lift of 5 seconds correlated with a NIF of -50 cm H₂O.
- Pavlin et. al. - At -25 cm H₂O or less NIF, no patient could swallow or maintain an airway.

How do we assess adequacy of reversal of neuromuscular blockade? (Joe's Rules)

- (1) Twitch Monitor – (2) Clinical Indicators – (3) Our understanding of the usual duration of action of a particular NMBA
- Rule 1 - If any one of the three indicators is not adequate, reversal is indicated.
- Rule 2 – If there are more than one anesthesia provider involved in the case, everyone must agree on the adequacy of reversal of neuromuscular blockade. If not, reversal is indicated.
- Rule 3 – The side effects of reversal agents are annoying, the complications of premature extubation could be deadly.

Should you reverse or not?

- Recovery is quicker and more reliable with intermediate acting agents.
- Lunn et. al. – 11 of 32 deaths due to anesthesia were secondary to post-operative respiratory failure. Neuromuscular blockade was a definite contributor in six of the cases.
- Tiret et. al. – 50% of 65 deaths due to anesthesia were related to post-operative respiratory failure.
- Cooper et. al. – 24 of 53 admissions to the ICU secondary to anesthesia related problems were secondary to post-operative respiratory failure and residual neuromuscular blockade.
- Baillard et. al. – With an increased use of quantitative measurements of neuromuscular blockade (TOF) and the use of reversal agents, residual blockade (TOF < 90%) decreased from 62% to 3% [between 1995 and 2004].
- Debaene et. al. – In patients not receiving reversal agents, a TOF ratio of < 0.7 occurred 37% of the time two hours after a single dose of NIMBA.
- Caldwell et. al. – They found a TOF < 0.7 up to 4 hours after a single intubating dose of vecuronium.
- Many today use a TOF > 90% (instead of > 70%) as an indicator of appropriate return of neuromuscular function.

Should you reverse or not? (continued)

- The surgical patient population is becoming older and will likely have the presence of concomitant disease both leading to a decreased clearance of the NMBAs.
- Furthermore, the population is becoming increasingly more debilitated when compared to a few years ago.
- Anesthetics are becoming shorter acting (e. g. remifentanyl, desflurane, sevoflurane and propofol), therefore, patients are fully awake more quickly.
- Surgeries are being done on an ambulatory basis at increasing rates, therefore, patients are expected to be awake, walk out of the center and be functional at home earlier.

Should you reverse or not?

- The benefits outweigh the risks of giving reversal agents in most situations.

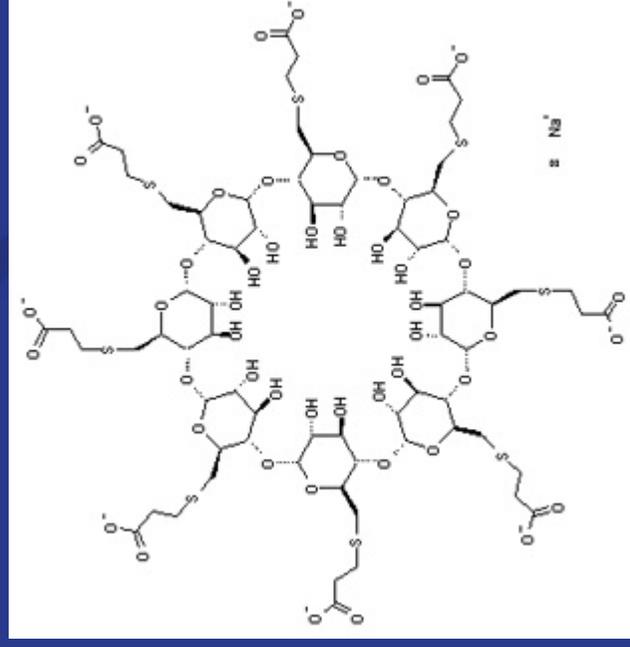
What do I frequently tell my teenagers?

“You can mess up anything if you try
hard enough!!”

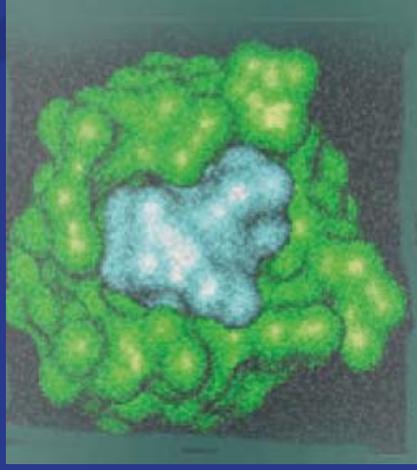
Org 25969 (Sugammadex)

- The 1st selective relaxant binding agent (SRBA)
- It is a synthetic cyclodextrin especially designed to bind the steroidal NMBA rocuronium
- Org 25969 causes a dose dependant fast recovery of neuromuscular blockade of rocuronium
- It is rapidly excreted by the kidneys
- The reversal of the neuromuscular blockade is dependent on the binding of the NMBA not the excretion of the drug by the kidneys
- There does not appear to be significant side effects with this drug.

Org 25969



Org 25969 (green) and Rocuronium (blue)



Org 25969 administered 5 minutes after 1.2 mg/kg of Rocuronium until

TOF > 90%

- placebo (n=4) 122:05
- 2.0 mg.kg-1 (n=5) 56:30 minutes
- 4.0 mg.kg-1 (n=5) 15:47 minutes
- 8.0 mg.kg-1 (n=12) 2:45 minutes
- 12.0 mg.kg-1 (n=7) 1:23 minutes
- 16.0 mg.kg-1 (n=7) 1:55 minutes
- Side Effects: Three patients had QT prolongation, but none were felt to be secondary to ORG 25969. Two reactions may have been secondary to ORG 25969; diarrhea and movement under light anesthesia.

[2005] [A1117] Reversal of Rocuronium-Induced (1.2 mg.kg-1) Neuromuscular Block by Org 25969: A Multi Center Dose Finding and Safety Study

“First Human Exposure of Org 25969, a Novel Agent to Reverse the Action of Rocuronium Bromide”. Gijssenbergh et. al.

Anesthesiology 2005; 103: 695-703

- 29 healthy males, Org 25969 vs. placebo, given 3 minutes after Rocuronium Bromide (0.6 mg/kg)
- Six different doses of Org 25969 were used (0.1 mg/kg to 0.8 mg/kg).
- Side effects included; dry mouth, fasciculations and paresthesias. None required treatment.
- Within 2 minutes, the patients receiving 8 mg/kg of Org 25969 reached a TOF ratio of > 0.9 within two minutes.
- **Conclusions:** Org 25969 was well tolerated and very effective in reversing Rocuronium Bromide in 29 human volunteers.

[Abstract A1119] Another study looking at Rocuronium (0.6 mg/kg) and Vecuronium (0.1 mg/kg)

- Rocuronium
 - Vecuronium
 - Placebo 31:48+/-21:00 (min:sec) 48:45+/-27:53
 - 0.5 mg/kg 3:40+/-1:02 7:43+/-2:34
 - 1.0 mg/kg 2:19+/-0:35 2:30+/-0:49
 - 2.0 mg/kg 1:43+/-0:36 2:15+/-0:48
 - 3.0 mg/kg 1:53+/-1:10 1:31+/-0:32
 - 4.0 mg/kg 1:07+/-0:18 1:24+/-0:28
- Side Effects: (rocuronium) tachycardia (vecuronium) abdominal pain, mild erythema, and delayed recovery from anesthesia

What if you have to reintubate (re-paralyze) after the use of Org 25969?

- Anton et. al. (ASA abstracts / A-1144 / 2004)
 - “After induction of neuromuscular blockade with rocuronium and rapid reversal with Org 25969, the **non-steroidal NMBA**s (atracurium, cis-atracurium, mivacurium and succinylcholine) were still potent and efficacious.”
 - “...showing that Org 25969 has a very low affinity for non-steroidal NMBA.s.”

(Sugammadex) Questions yet to be answered:

- Would **Sugammadex** be equally as effective after a prolonged infusion of vecuronium or rocuronium in the ICU, or even repeated doses in the OR?
- What dose of **Sugammadex** is required in an elderly severely ill patient, a patient with electrolyte abnormalities, or a patient on multiple medications known to potentiate NMBAs?

**“Reversal of Neuromuscular
Blockade”; Anesthesiology, 77: 785-
805, 1992 (Bevan et. al.)**

Questions anyone?

