Pharmacology of the Neuromuscular Junction (NMJ)

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Autonomic Nervous System

NERVOUS SYSTEM

- Central Nervous System
- Afferent Division
- Somatic Voluntary
- Sympathetic Nervous System
- Parasympathetic Nervous System

Peripheral Nervous System

Efferent Division

Autonomic Nervous System

- Autonomic Involuntary
- Visceral Vegetative

FUNCTIONS CONTROLLED

- Respiration
- Circulation
- Body Temperature
- Metabolism
- Sweating
- Secretions

PARASYMPATHETIC
- Cranial N. III, VII, IX, X
- Sacral S2-5
- "Feeding & Breeding"
- IBP, IHR, TGT

SYMPATHETIC
- Thoracolumbar T1-12, L1-3
- "Flight or Fight"
- IBP, THR, IGT

PARASYMPATHETIC
- Craniosacral

CENTRAL INVOLVEMENT
- Hypothalamus - Integration, body temp & water balance
- Medulla - BP, respiration
- Cerebral cortex - somatic NS & ANS integration
Neurons of the ANS

- Medulla
- ACh N
- ACh M
- Cardiac and smooth muscle, gland cells, nerve terminals
- Sweat glands
- NE αβ
- Cardiac and smooth muscle, gland cells, nerve terminals
- Renal vascular smooth muscle
- Adrenal medulla
- Epi, NE
- ACh N
- Skeletal muscle
- Somatic

Neuromuscular Junction

**FIG. 20 The Motor Endplate**

- MYELIN SHEATH
- AXON
- NODE OF RANVIER
- TERMINAL MEMBRANE
- SUBNEURAL SPACE
- POSTJUNCTIONAL MEMBRANE
- SCHWANN CELL
- MITOCHONDRIA
- MYOFIBRILS
- NUCLEUS
- SARCOPLASMA
- Transverse Tubular System (TTS)

- NERVE ACTION POTENTIAL (AP)
- ACETYLCHOLINE RELEASE
- DEPOLARIZATION (EPP) (INCREASED PERMEABILITY TO Na⁺ AND K⁺)
- MUSCLE ACTION POTENTIAL (MAP)
- SPREAD OF EXCITATION IN MUSCLE VIA TTS
- MUSCLE CONTRACTION
Myasthenia gravis
Autoimmune disease

1:10,000 (250,000 USA)
• antibodies to NMJ nicotinic receptors leads to degradation
• simplified synaptic folds
• normal nerve terminal and transmitter
• wider synaptic junction

Diagnosis: Edrophonium (Tensilon, short acting) is used for diagnosis and determination of maintenance dose

Treatment: Neostigmine has direct (stimulates receptor) and indirect actions (inhibition of AchE). No CNS activity.

NMJ Nicotinic Receptor

Ion Channel
• pentamer
• Na⁺ in
• K⁺ out

Infant: α₂βδε
Adult: α₂βδγ
NMJ Blocking Agents

Paralysis: small rapidly moving muscles (eyes, fingers), then limbs, last is respiratory muscles (recovery in reverse order)

- **Competitive (non-depolarizing) agents (curare)**
  - compete with Ach for binding to receptor
  - flaccid, relaxed paralysis
  - non-NMJ effects: ganglia, muscarinic blocking, histamine release
  - NMJ block can be reversed by AchE inhibitors

- **Non-competitive (depolarizing) agents (succinylcholine)**
  Phase 1 block:
  - membrane depolarization
  - transient fasciculations followed by paralysis
  Phase 2 block:
  - desensitization
  - membrane repolarizes, hyposensitive to Ach
  - NMJ block not reversed by AchE inhibitors
Competitive (nondepolarizing) Blocking Agents - Curare

- **Tubocurarine, dimethyltubocaraine (metocarine)**
  - no effect on nerve transmission
  - muscle can still be stimulated
  - 5-10mg (iv) produces flaccid paralysis
  - 10-20mg (iv) can produce apnea, not active orally
  - can cause histamine release (mast cells)
  - can block ganglionic receptors [higher concentrations]

A Amazon hunter tips his darts with the poison curare

Competitive (nondepolarizing) Blocking Agents - Others

- **Pancuronium**
  - more potent than tubocurarine (x5)
  - reduced histamine release than curare
  - lack of ganglionic blockade

- **Gallamine**
  - also some muscarinic block

- **Mivacurium**
  - fast onset (2-4min), short acting (12-18min), hydrolysis by AchE, some histamine release

- **Rocuronium**
  - fast onset (1-2min), 30-40min duration, hypersensitivity

- **Atracurium**
  - hydrolysis by AchE
**Adverse Effects and Treatment**

- **Adverse effects:**
  - apnea (loss of respiration)
  - ganglionic blockade (tubocurarine)
  - histamine release (tubocurarine)
  - muscarinic block (gallamine)
  - hypotension (histamine release & ganglionic block)
  - no significant CNS effects

- **Treatment of toxicity:**
  - Acetylcholinesterase inhibitors ie. neostigmine

**Depolarizing NMJ Blocking Agents**

- **Succinylcholine** (decamethonium, not used)
  - Phase 1: depolarization, Phase 2: desensitization
  - brief duration (5-10min)
  - metabolized by pseudocholinesterase
  - 'atypical' pseudo-AchE (1:10,000, long-lasting)
  - less histamine release than curare
  - less effect at ganglia than curare
  - not reversed by AchE inhibitors
Succinylcholine: Adverse effects & treatment

- **Toxicity:**
  - similar to competitive blockers with less effects at ganglia or histamine release

- **Treatment:**
  - Artificial respiration
  - use of AChE inhibitors will not reverse NMJ blockade

- **Adverse reactions:**
  - ‘Atypical’ psuedo-AchE (1:10,000, prolonged apnea, 2-3hr)
  - Hyperkalemia (esp. burn, trauma patients, response delayed 2-7 days)
  - Malignant hyperthemia (esp. with halothane)

**Hyperkalemia**

- burn & trauma
- usually small ↑K+
- cardiac arrest
- support: dialysis glucose / insulin

![Hyperkalemia Graph](image)
Malignant Hyperthermia

- more likely with halothane
- 60% mortality
- $\uparrow$ Ca$^{++} \rightarrow \uparrow$ body temp
- tachycardia
- dysrhythmia
- $\uparrow$ HR, muscle rigidity

Treatment:
- Dantrolene
- drug of choice
- $\downarrow$ Ca$^{++}$ release

Clinical Uses of NMJ Blocking Agents

- **Muscle relaxation in surgery**
  - decreases depth of anesthesia
- **Orthopedics**
  - dislocations, alignment of fractures
- **Facilitate intubations**
  - in mechanical artificial ventilation
- **Facilitate internal examinations**
  - laryngoscopy, bronchoscopy, esophagoscopy
- **Prevent trauma**
  - during electroshock therapy
- **Diagnostic**
  - tubocurarine (Myasthenia gravis), not commonly used
  - not recommended, Edrophonium (Tensolin) better
NMJ Agents: Drug Interactions

Synergism with certain agents → ↓ dose

Calcium channel blockers ie. verapamil
- ↓ Ach release

Aminoglycoside antibiotic ie. neomycin
- compete with Ca++
- ↓ Ach release & stabilize membrane

Certain general anesthetic ie. halothane
- stabilize membrane

Direct Acting Neuromuscular Relaxant

• **Dantrolene (Dantrium)**
  - inhibits calcium release
  - significant liver toxicity
  - muscle weakness

• **Clinical uses:**
  - stroke
  - cerebral palsy
  - malignant hyperthermia (DOC)
  - multiple sclerosis

• **Other agents**
  - Benzodiazepines
Future Directions

1. Sugammadex (ORG 25969, Selective Relaxant Binding Agent (SRBD), Phase III clinical trials):
   - forms tight complex with steroidal NMBs, binds to drug, no effect on acetylcholinesterase or any receptor system.
     Rocuronium > Vecuronium >> Pancuronium
   - ineffective against succinylcholine, atracurium, mivacurium

2. Gantacurium (Non-depolarizing, competitive NMB, Phase II clinical trials)
   - rapid onset (1-2 min), short duration (10-15 min)
   - metabolism by ester hydrolysis and cysteine adduction

Sugammadex: Chemical Structure

- ORG 25969
- note polar, hydroxyl groups
- hydrophobic cavity traps drug-results in formation of a water soluble guest host complex
- “Encapsulates” rocuronium molecule
- Allows “Rapid Reversal”
- Phase III Clinical trials
- Renal elimination
- Excreted unchanged in first 8 hours

Rocuronium
Sugammadex: Human trial

Baseline - Non-Paralyzed

![Graph showing the effect of sugammadex on twitch percentage over time.](image)

*deBoer, HD, et al. Anesthesiology, 104:718-723 2006*

Recovery (Succinylcholine vs Rocuronium)

If you must reestablish nm blockade….
And you used sugammadex….
What should you use???

Ineffective against succinylcholine and NMBs (mivacurium, atracurium, and cisatracurium)

*Naguib M., Anesthesia & Analgesia, Vol 104, No 3, March 2007*
Gantacurium (GW 280430 A)

- By GSK, similar to Mivacurium
- ED 95 = 0.18 mg/kg
- Onset 1.2 - 1.8 min & duration of 15 min
- Higher doses cause histamine release without change in onset time
- Alkaline hydrolysis in plasma + spontaneous formation of cysteine adducts
- Very little genetic variability

Comparison of Competitive (d-Tubocurarine) and Non-competitive, depolarizing (Succinylcholine) Agents

<table>
<thead>
<tr>
<th></th>
<th>Tubocurarine</th>
<th>Succinylcholine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase I</td>
<td>Phase II</td>
</tr>
<tr>
<td>Addition of succinylcholine</td>
<td>Antagonistic</td>
<td>Additive</td>
</tr>
<tr>
<td>Addition of tubocurarine</td>
<td>Additive</td>
<td>Antagonistic</td>
</tr>
<tr>
<td>Effect of neostigmine</td>
<td>Reverse</td>
<td>Augmented</td>
</tr>
<tr>
<td>Initial effect on striated muscle</td>
<td>None</td>
<td>Fasciculations</td>
</tr>
<tr>
<td>Response to tetanic stimulation</td>
<td>Unsustained</td>
<td>Sustained</td>
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</tbody>
</table>
# NMJ Blocking Agents – Other Actions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ganglia</th>
<th>Muscarinic Receptors</th>
<th>Histamine Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>Stimulates</td>
<td>Stimulates</td>
<td>Slight</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>Blocks</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td>Metaocurine</td>
<td>Blocks weakly</td>
<td>None</td>
<td>Slight</td>
</tr>
<tr>
<td>Gallamine</td>
<td>None</td>
<td>Blocks strongly</td>
<td>None</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>None</td>
<td>Blocks weakly</td>
<td>None</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Atracurium</td>
<td>None</td>
<td>None</td>
<td>Slight</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>None</td>
<td>None</td>
<td>Slight</td>
</tr>
</tbody>
</table>

# Onset, Duration and Elimination of Neuromuscular Blocking Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset (min)</th>
<th>Duration (min)</th>
<th>Mode of elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>1-2</td>
<td>6-8</td>
<td>Hydrolysis by AchE</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td>Metaocurine</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney</td>
</tr>
<tr>
<td>Gallamine</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>2-4</td>
<td>30-40</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td>Atracurium</td>
<td>2-4</td>
<td>30-40</td>
<td>Hydrolysis by AchE</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>1-2</td>
<td>30-40</td>
<td>Liver</td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>2-4</td>
<td>80-100</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>2-4</td>
<td>12-18</td>
<td>Hydrolysis by AChE</td>
</tr>
</tbody>
</table>
Succinylcholine

"Boy! That new sleeping drug really works fast!"
Rapid onset and short duration, this sucks!
What are we going to name it?

Neuromuscular Blockade Variables

Time to 25% recovery
Onset
Recovery Index

Time to 95% recovery