Pharmacology of the Neuromuscular Junction (NMJ)
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Drugs of the Autonomic Nervous System

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: \( \alpha_2\beta\delta\epsilon \)
Adult: \( \alpha_2\beta\delta\gamma \)
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, dimethyltubocarine (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]

Amazon hunter tips his darts with the poison curare

Competitive (nondepolarizing) NMBs - Others
- Pancuronium
  - more potent than tubocurarine (x5)
  - reduced histamine release than curare
  - lack of ganglionic blockade
- Rocuronium
  - fast onset (1-2min), 30-40min duration, hypersensitivity
- Atracurium (~10 isomers)
  - hydrolysis by AchE
  - replaced by cisatracurium, Hofmann degradation, organ independent
- Gallamine
  - also some muscarinic block
- Mivacurium
  - fast onset (2-4min), short acting (12-18min), hydrolysis by AchE, some histamine release

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
  - fast onset (<1min), 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

FIG. 21

FIG. 22

FIG. 23
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' pseudo-AchE (1:10,000; prolonged apnea, 2-3hr)
  - Hyperkalemia (esp. burn, trauma patients, response delayed 2-7 days)
  - Malignant hyperthermia (esp. with halothane)

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**Hyperkalemia**

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

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**Malignant Hyperthermia**

- more likely with halothane
- 60% mortality
- ↑Ca++ → ↑ body temp 
- tachycardia
- dysrhythmia
- ↑HR, muscle rigidity

Treatment:
- Dantrolene
  - drug of choice
  - ↓Ca++ release

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**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

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**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

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

<table>
<thead>
<tr>
<th>Tubocurarine</th>
<th>Succinylcholine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Phase II</td>
</tr>
<tr>
<td>Addition of succinylcholine</td>
<td>Antagonistic</td>
</tr>
<tr>
<td>Addition of tubocurarine</td>
<td>Additive</td>
</tr>
<tr>
<td>Effect of neostigmine</td>
<td>Reverse</td>
</tr>
<tr>
<td>Initial effect on striated muscle</td>
<td>None</td>
</tr>
<tr>
<td>Response to tetanic stimulation</td>
<td>Unsustained</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>NMJ Blocking Agents – Other Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganglia</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Succinylcholine</td>
</tr>
<tr>
<td>Tubocurarine</td>
</tr>
<tr>
<td>Metaocurine</td>
</tr>
<tr>
<td>Gallamine</td>
</tr>
<tr>
<td>Pancuronium</td>
</tr>
<tr>
<td>Vecuronium</td>
</tr>
<tr>
<td>Atracurium</td>
</tr>
<tr>
<td>Rocuronium</td>
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<tr>
<td>Mivacurium</td>
</tr>
</tbody>
</table>

Onset, Duration and Elimination of Neuromuscular Blocking Drugs

<table>
<thead>
<tr>
<th>Neuromuscular Blocking Drugs</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>90-120</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td>Metaocurine</td>
<td>4-6</td>
<td>90-120</td>
<td>Kidney</td>
</tr>
<tr>
<td>Gallamine</td>
<td>4-6</td>
<td>90-120</td>
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<td>Pancuronium</td>
<td>4-6</td>
<td>90-120</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>cisAtracurium</td>
<td>2-4</td>
<td>30-40</td>
<td>Hofmann degradation</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>90-100</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>2-4</td>
<td>12-18</td>
<td>Hydrolysis by AchE</td>
</tr>
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