Pharmacology of the Neuromuscular Junction (NMJ)

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Neuromuscular Junction

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

NMJ Nicotinic Receptor

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

  Infant: α₂βδε
  Adult: α₂βδγ

Competitive (nondepolarizing) Blocking Agents - Curare

- Tubocurarine, dimethyltubocarine (metocarinate)
  - 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, hypersenstivity

- **Atracurium** (~10 isomers)
  - hydrolysis by AchE
  - replaced by cisatracurium, Hoffmann degradation, organ independent

- **Gallamine**
  - also some muscarinic block

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

**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 hyperthermia (esp. with halothane)

**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

**Malignant Hyperthermia**

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

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

**Hyperkalemia**

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

- [K⁺] Hyperkalemia

- ↑K⁺ → cardiac arrest
- support: dialysis glucose / insulin
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

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

<table>
<thead>
<tr>
<th>Tubocurarine</th>
<th>Succinylcholine</th>
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<tbody>
<tr>
<td>Phase I</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Addition of succinylcholine
- Antagonistic
- Additive
- Augmented

Addition of tubocurarine
- Additive
- Antagonistic
- Augmented

Effect of neostigmine
- Reverse
- Augmented
- Antagonistic

Initial effect on striated muscle
- None
- Fasciculations
- None

Response to tetanic stimulation
- Unsustained
- Sustained
- Unsustained

Synergism with certain agents → ↓ dose

- Calcium channel blockers ie. verapamil
  - ↓ Ach release
- Aminoglycoside antibiotic ie. neomycin
  - compete with Ca^{2+}
  - ↓ Ach release & stabilize membrane
- Certain general anesthetic ie. halothane
  - stabilize membrane

NMJ Agents: Drug Interactions

**Direct Acting Neuromuscular Relaxant**

- **Dantrolene (Dantrium)**
  - inhibits calcium release from SR
  - significant liver toxicity
  - muscle weakness
- **Clinical uses:**
  - stroke
  - cerebral palsy
  - malignant hyperthermia (DOC)
  - multiple sclerosis
- **Other agents**
  - Benzodiazepines

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>
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</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>
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<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>
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<td>2-4</td>
<td>30-40</td>
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<td>Rocuronium</td>
<td>1-2</td>
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<td>Liver</td>
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<td>Pipecuronium</td>
<td>2-4</td>
<td>80-100</td>
<td>Kidney, Liver</td>
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