Pharmacology of the Neuromuscular Junction (NMJ)

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Neuromuscular Junction
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 (metocarina)**
  - 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, Hoffmann degradation, organ independent

- **Gallamine**
  - also some muscarinic block

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

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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

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)
**Hyperkalemia**

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

**Malignant Hyperthermia**

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

**Treatment:**
- Dantrolene
- drug of choice
- ↓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 from SR
  - 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></th>
<th>Tubocurarine</th>
<th>Succinylcholine</th>
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</thead>
<tbody>
<tr>
<td>Phase I</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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### NMJ Blocking Agents – Other Actions

<table>
<thead>
<tr>
<th></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>cisAtracurium</td>
<td>2-4</td>
<td>30-40</td>
<td>Hoffmann 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>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>
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