Pharmacology of the Neuromuscular Junction (NMJ)

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Autonomic Nervous System

Neurons of the ANS

Neuromuscular Junction

NMJ Nicotinic Receptor

NMJ Blocking Agents

- 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 followed by paralysis
  - Phase 2 block: desensitization
  - NMJ block not reversed by AchE inhibitors

**Competitive (nondepolarizing) Blocking Agents - Curare**
- Tubocurarine, dimethylytubocarbine (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 [high concentration]

- 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
  - short acting, hydrolysis by AchE
- Atracurium
  - short acting, hydrolysis by AchE

**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)
  - 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
- significant liver toxicity
- muscle weakness
- Clinical uses:
  stroke
cerebral palsy
malignant hyperthermia (DOC)
multiple sclerosis
- Other agents
Benzodiazepines

NMJ – Competitive vs Non Competitive

Comparison of Competitive (d-Tubocurarine) and
Depolarizing (Succinylcholine) Agents

| NMJ – Competitive vs Non Competitive |
| Comparison of Competitive (d-Tubocurarine) and Depolarizing (Succinylcholine) Agents |
NMJ Blocking Agents – Other Actions

<table>
<thead>
<tr>
<th></th>
<th>Ganglia</th>
<th>Muscarinic Receptors</th>
<th>Histamine Release</th>
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</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
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<tr>
<td>Tubocurarine</td>
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<td>Metaocurine</td>
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<td>Gallamine</td>
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<td>Pancuronium</td>
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<td>Vecuronium</td>
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<td>Doxacurium</td>
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<td>Pipecuronium</td>
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<td>Mivacurium</td>
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NMJ – Onset, Duration & Elimination

Onset, Duration and Elimination of Neuromuscular Blocking Drugs

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<thead>
<tr>
<th></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>
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<tr>
<td>Tubocurarine</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney, liver</td>
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<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>
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</tr>
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<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>
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<td>Atracurium</td>
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<td>30-40</td>
<td>Hydrolysis by AchE</td>
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<tr>
<td>Doxacurium</td>
<td>4-6</td>
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<tr>
<td>Mivacurium</td>
<td>2-4</td>
<td>12-18</td>
<td>Hydrolysis by AChE</td>
</tr>
</tbody>
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Succinylcholine

"Good. That new sleeping drug really works, Matt!"

"Rapid onset and short duration, this suits! What are we going to name it?"