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
  - 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 (metocarline)
  - 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]

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

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' 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

![Hyperkalemia](image)

**Malignant Hyperthermia**

- more likely with halothane
- 60% mortality
- ↑Ca++ → ↑ body temp
- tachycardia
dysrhythmia
- THR, 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**

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### NMJ Blocking Agents – Other Actions

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<tr>
<th></th>
<th>Ganglia</th>
<th>Muscarinic Receptors</th>
<th>Histamine Release</th>
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<tbody>
<tr>
<td>Succinylcholine</td>
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<tr>
<td>Tubocurarine</td>
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### NMJ – Onset, Duration & Elimination

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<thead>
<tr>
<th>Onset (min)</th>
<th>Duration (min)</th>
<th>Mode of elimination</th>
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<tbody>
<tr>
<td>Succinylcholine</td>
<td>1-2</td>
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<tr>
<td>Tubocurarine</td>
<td>4-6</td>
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<tr>
<td>Metaocurine</td>
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<td>80-120</td>
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<td>Gallamine</td>
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