Muscle Relaxants
Neuromuscular Junction

The Neuromuscular Junction

Diagram showing the components and processes of the neuromuscular junction. The diagram includes labels for the axon of a motor neuron, myelin sheath, action potential, terminal button, axon terminal, voltage-gated calcium channel, vesicle of acetylcholine, voltage-gated Na+ channel, plasma membrane of muscle fiber, acetylcholine receptor site, acetylcholinesterase, neurotransmitter-gated channel, motor end plate, muscle fiber, and action potential propagation in muscle fiber.
• Cholinergic antagonists

➤ **Neuromuscular-blocking agents** (mostly nicotinic antagonists): interfere with transmission of **efferent impulses** to skeletal muscles.

• These agents are used as **skeletal muscle relaxant** adjuvants in anesthesia during surgery, intubation, and various orthopedic procedures.
# NEUROMUSCULAR BLOCKERS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
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<tbody>
<tr>
<td>Cisatracurium</td>
<td>NIMBEX</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>PAVULON</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>ZEMURON</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>ANECTINE, QUELICIN</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>ONLY GENERIC</td>
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Neuromuscular-blocking agents

• These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle

• They possess some chemical similarities to ACh, and they act either as
  • Antagonists (Nondepolarizing type)
  • Agonists (Depolarizing type) at the receptors on the endplate of the NMJ.
• Neuromuscular blockers are clinically useful during surgery to facilitate
• Tracheal intubation to provide complete muscle relaxation at lower anesthetic doses allowing for:
  ✓ More rapid recovery from anesthesia.
  ✓ Reducing postoperative respiratory depression.
A. Nondepolarizing (competitive) blockers

- The first drug known to block the skeletal NMJ was *curare* [kyoo- RAH-ree], which native South American hunters of the Amazon region used to paralyze prey.
- The development of the drug *tubocurarine* [too-boe-kyoo-AR-een] followed, but it has been replaced by other agents with fewer adverse effects, such as
  - *Cisatracurium* [cis-a-trah-cure-ih-um],
  - *Pancuronium* [pan-kure-oh-nee-um],
  - *Rocuronium* [roe-kyoor-oh-nee-um],
  - *Vecuronium* [ve-KYOOroe-nee-um].
• The neuromuscular-blocking agents have significantly increased the safety of anesthesia, because less anesthetic is required to produce muscle relaxation, allowing patients to recover quickly and completely after surgery.

• Neuromuscular blockers should not be used to substitute for inadequate depth of anesthesia.
Mechanism of action:

a. At low doses: Nondepolarizing agents competitively block ACh at the nicotinic receptors

- They compete with ACh at the receptor without stimulating it.
- These drugs prevent depolarization of the muscle cell membrane and inhibit muscular contraction.
- Their competitive action can be overcome by administration of cholinesterase inhibitors, such as neostigmine and edrophonium, which increase the concentration of ACh in the neuromuscular junction.
- Anesthesiologists employ this strategy to shorten the duration of the neuromuscular blockade. In addition, at low doses the muscle will respond to direct electrical stimulation from a peripheral nerve stimulator to varying degrees, allowing for monitoring of the extent of neuromuscular blockade.
Mechanism of action

- **Rocuronium**
- **Acetylcholine**
- **Na^+**

Nicotinic receptor at neuromuscular junction
b. **At high doses:** Nondepolarizing agents can block the ion channels of the motor endplate. This leads to **further weakening** of neuromuscular transmission, thereby reducing the ability of cholinesterase inhibitors to reverse the actions of the nondepolarizing blockers.

- With complete blockade, the muscle does not respond to direct electrical stimulation.
Actions:

• Not all muscles are equally sensitive to blockade by competitive agents.

• **Small, rapidly contracting muscles** of the face and eye are most susceptible and are paralyzed first, followed by the fingers, limbs, neck, and trunk muscles.

• Next, the **intercostal muscles** are affected and, lastly, the diaphragm.
Pharmacokinetics:

• These agents possess two or more quaternary amines in their bulky ring structure that prevent their absorption from the gut.

• They penetrate membranes very poorly and do not enter cells or cross the blood–brain barrier.

• Many of the drugs are not metabolized, and their actions are terminated by redistribution.

Figure 5.10
Pharmacokinetics of the neuromuscular-blocking drugs. IV = intravenous.
Cisatracurium spontaneously degrades in plasma and is the only nondepolarizing neuromuscular blocker whose dose need not be reduced in patients with renal failure. It is often used in patients with multisystem organ failure because its metabolism is independent of hepatic or renal function. Cisatracurium is useful in mechanical ventilation of critically ill patients.
Drug interactions:

a. **Cholinesterase inhibitors**: Drugs such as neostigmine physostigmine, pyridostigmine, and edrophonium can overcome the action of nondepolarizing neuromuscular blockers.
   - With increased dosage, cholinesterase inhibitors can cause a **depolarizing block** as a result of elevated ACh concentrations at the endplate membrane.
   - If the neuromuscular blocker has entered the ion channel, cholinesterase inhibitors are not as effective in overcoming blockade.

b. **Halogenated hydrocarbon anesthetics**: Drugs such as desflurane act to enhance neuromuscular blockade by exerting a stabilizing action at the NMJ.
   - These agents sensitize the NMJ to the effects of neuromuscular blockers.

c. **Aminoglycoside antibiotics**: Drugs such as gentamicin and tobramycin inhibit ACh release from cholinergic nerves by competing with calcium ions. They synergize with pancuronium and other competitive blockers, enhancing the blockade.
B. Depolarizing agents

- Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh.

- These agents are more resistant to degradation by acetylcholinesterase (AChE) and can thus more persistently depolarize the muscle fibers.

- **Succinylcholine** [suk-sin-il-KOE-leen] is the only depolarizing muscle relaxant in use today.
• The depolarizing agent first causes the opening of the sodium channel associated with the nicotinic receptors, which results in depolarization of the receptor (Phase I). This leads to a transient twitching of the muscle (fasciculations).

• **Continued binding** of the depolarizing agent renders the receptor incapable of transmitting further impulses.

• With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (Phase II) and flaccid paralysis.
PHASE I
Membrane depolarizes, resulting in an initial discharge that produces transient fasciculations followed by flaccid paralysis.

PHASE II
Membrane repolarizes, but receptor is desensitized to the effect of acetylcholine.
Actions:

• As with the competitive blockers, the respiratory muscles are paralyzed last.

• Succinylcholine initially produces brief muscle fasciculations that cause muscle soreness. This may be prevented by administering a small dose of nondepolarizing neuromuscular blocker prior to succinylcholine.

• Normally, the duration of action of succinylcholine is extremely short, due to rapid hydrolysis by plasma pseudocholinesterase.

• Succinylcholine that gets to the NMJ is not metabolized by AChE, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes).
Therapeutic uses

• Because of its rapid onset of action, succinylcholine is useful when rapid endotracheal intubation is required during the induction of anesthesia (a rapid action is essential if aspiration of gastric contents is to be avoided during intubation).

• It is also used during electroconvulsive shock treatment.
Pharmacokinetics

- *Succinylcholine* is injected intravenously.
- Its brief duration of action results from redistribution and rapid hydrolysis by plasma pseudocholinesterase.
- It is sometimes given by continuous infusion to maintain a longer duration of effect.
- Drug effects rapidly disappear upon discontinuation.
Adverse effects:

• **Hyperthermia**: Succinylcholine can potentially induce malignant hyperthermia (MH) in susceptible patients.

• (MH) a rare life-threatening condition. causes a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, overwhelming the body’s capacity to supply oxygen, remove carbon dioxide, and regulate temperature, eventually leading to circulatory collapse and death if not treated immediately.
b. Apnea: Administration of succinylcholine to a patient who is deficient in plasma cholinesterase or who has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm.

The rapid release of potassium may also contribute to prolonged apnea in patients with electrolyte imbalances who receive this drug. In patients with electrolyte imbalances who are also receiving digoxin or diuretics (such as heart failure patients) succinylcholine should be used cautiously or not at all.

c. Hyperkalemia: Succinylcholine increases potassium release from intracellular stores. This may be particularly dangerous in burn patients and patients with massive tissue damage in which potassium has been rapidly lost from within cells.
Postoperative muscle pain is common; hyperkalemia and increased intraocular and intragastric pressure may occur. Drug may trigger malignant hyperthermia. Rapid onset makes succinylcholine useful for tracheal intubation in patients with gastric contents.
Spasmylyric

• At high doses, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord, where the $\alpha2$-GABA$\alpha$ receptors are largely located.

• Diazepam is useful in the treatment of skeletal muscle spasms, such as occur in muscle strain, and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

• Baclofen [BAK-loe-fen] is a muscle relaxant that is believed to affect GABA receptors at the level of the spinal cord.