Pharmacology Summarization

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Chapter 48
**Cholinergic antagonist**

- Cholinergic antagonist is a general term for agents that bind to cholinoreceptors (muscarinic or nicotinic) and **prevent** the effects of acetylcholine (ACh) and other cholinergic agonists.

- They are commonly known as anticholinergic agents, **antimuscarinic agents** (more accurate terminology), or parasympatholytics.

- these agents (for example, atropine and scopolamine) block muscarinic receptors, causing inhibition of muscarinic functions.

- In addition, these drugs block the few exceptional sympathetic neurons **that are cholinergic**, such as those innervating the salivary and sweat glands.

- the antimuscarinic drugs have **little or no action** at skeletal neuromuscular junctions (NMJs) or autonomic ganglia.

**A. Atropine:**

- is a tertiary amine belladonna alkaloid with a high affinity for muscarinic receptors.
- It binds competitively and prevents ACh from binding to those sites.
- Its general actions last about 4 hours, except when placed topically **in the eye**, where the action may last for days.
- The greatest inhibitory effects are on **bronchial tissue** and the secretion of **sweat and saliva**.
1. **Actions:**

   a. **Eye:**
   - Resulting in: 1- mydriasis   2-unresponsiveness to light   
   3-cycloplegia (inability to focus for near vision).
   - In patients with angle-closure glaucoma, intraocular pressure may rise dangerously.

   B. **Gastrointestinal (GI):**
   - Atropine can be used as an antispasmodic to reduce activity of the GI tract.
   - gastric motility is reduced
   - atropine is not effective for the treatment of peptic ulcer
   - atropine that reduce spasms also reduce saliva secretion, ocular accommodation, and urination.

   c. **Cardiovascular:**
   - Atropine produces divergent effects on the cardiovascular system, depending on the dose.
   
   # At low doses: slight decrease in heart rate (by M1 receptor).
   # At High doses: progressive increase in heart rate (by M2 receptor).

   d. **Secretions:**
   - Atropine blocks muscarinic receptors in the salivary glands, producing dryness of the mouth (xerostomia).
   - Inhibition secretion of Sweat and lacrimal glands.

2. **Therapeutic uses:**
a. **Ophthalmic**: Topical atropine exerts both *mydriatic* and *cycloplegic* effects, and it permits the measurement of refractive errors without interference by the accommodative capacity of the eye. *Shorter*-acting antimuscarinics have *largely replaced* atropine due to prolonged mydriasis observed with atropin.

b. **Antispasmodic**: Atropine is used as an *antispasmodic* agent to relax the GI tract.

c. **Cardiovascular**: The drug is used to treat *bradycardia*.

d. **Antisecretory**: Atropine is sometimes used as an antisecretory agent to block secretions in the *upper and lower respiratory tracts* prior to surgery.

e. **Antidote for cholinergic agonists**: Atropine is used for the treatment of *organophosphate poisoning*, of overdose of anticholinesterases, and in some types of *mushroom poisoning*.

3. **Pharmacokinetics**:
   - Atropine is readily absorbed
   - partially metabolized by the liver
   - eliminated primarily in urine.

4. **Adverse effects**: Depending on the dose.
   - atropine may cause dry mouth
   - blurred vision
   - tachycardia
   - urinary retention
   - constipation.

   **Effects on the CNS include**: restlessness, confusion, hallucinations, and delirium, collapse of the circulatory and respiratory systems, and death.

   Low doses of cholinesterase inhibitors may be used to overcome atropine toxicity.

**B. Scopolamine**

- tertiary amine plant alkaloid.
- scopolamine has greater action on the CNS (unlike atropine, CNS effects are observed at therapeutic doses)
- longer duration of action as compared to atropine.

1. Actions:
- anti-motion sickness drugs
- unusual effect of blocking short-term memory.
- produces sedation (at higher doses produce excitement).

2. Therapeutic uses:
- prevention of motion sickness
- postoperative nausea and vomiting.

*For motion sickness, it is available as a topical patch that provides effects for up to 3 days.

3. Pharmacokinetics and adverse effects: These aspects are similar to those of atropine.

C. Ipratropium and tiotropium Ipratropium
- quaternary derivatives of atropine.
- These agents are approved as bronchodilators for maintenance treatment of bronchospasm.
- Both agents are delivered via inhalation. Because of their positive charges, these drugs do not enter the systemic circulation or the CNS.

D. Tropicamide and cyclopentolate
- These agents are used as ophthalmic solutions for mydriasis and cycloplegia.
- Their duration of action is shorter than that of atropine.

E. Benztropine and trihexyphenidyl
- useful as adjuncts to treat Parkinson’s disease and other types of parkinsonian syndromes.
Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium chloride

- These synthetic atropine. By blocking muscarinic receptors in the bladder, intravesical pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced.

Side effects include:
- dry mouth
- constipation
- blurred vision

Oxybutynin is available as a transdermal system (topical patch), which is better tolerated because it causes less dry mouth than oral formulations. The overall efficacies of these antimuscarinic drugs are similar.
GANGLIONIC BLOCKERS

Ganglionic blockers specifically act on the nicotinic receptors of both para-sympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor.

# ganglionic blockade is rarely used therapeutically, but often serves as a tool in experimental pharmacology.

A- NICOTINE:

# is a poison
# it is without therapeutic benefit and is deleterious to health
# Depending on the dose, nicotine depolarizes autonomic ganglia, resulting first in stimulation (increased release of neurotransmitters) and then in paralysis of all ganglia.
# The overall response of a physiologic system includes increased blood pressure and cardiac rate, and increased peristalsis and secretions
# at higher doses, the blood pressure falls because of ganglionic blockade, and activity in both GI tract and bladder musculature ceases
# NM-blocking agents have significantly increased the safety of anesthesia, because less anesthetic is required to produce muscle relaxation

NEUROMUSCULAR-BLOCKING AGENTS

They possess some chemical similarities to ACh, and they act either as antagonists (non-depolarizing) or agonists (depolarizing) at the receptors on the endplate of the NMJ. Neuromuscular blockers are clinically useful during surgery to facilitate tracheal intubation and provide complete muscle relaxation at lower anesthetic doses.

A- Nondepolarizing blockers (competitive)

Ex: cisatracurium, pancuronium and vecuronium

1- Mechanism of action:

a. at low doses: blocks ACh at the nicotinic receptors. That is, they compete with ACh at the receptor without stimulating it.

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. This strategy is employed 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.
b. **At high doses:** 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 competitive blockers. With complete blockade, the muscle does not respond to direct electrical stimulation.

2- Actions:
Not all muscles are equally sensitive to blockade by competitive agents. Small, rapidly contracted muscles of the face and eye are most susceptible and are paralyzed first, and then fingers, limbs, and so on, and lastly the diaphragm. The muscles recover in the reverse manner.

3- Pharmacokinetics:
All neuromuscular-blocking agents are injected intravenously or occasionally intramuscularly.

- **Pancuronium** is excreted unchanged in urine (most drugs excreted primarily unchanged in urine)
- **Cisatracurium** is degraded spontaneously in plasma and by ester hydrolysis.
- **Atracurium** releases histamine and is metabolized to **laudonosine**, which can provoke seizures.
- **Cisatracurium** which has the same pharmacokinetic properties as **atracurium**, is less likely to have those effects.

4- adverse effects:
In general, these agents are safe with minimal side effects

5- Drug interactions:

- **Cholinesterase inhibitors:** like neostigmine, physostigmine, pyridostigmine and edrophonium can overcome the action of nondepolarizing neuromuscular blockers. However, 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 MNJ 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 blockage.

D- **Calcium channel blockers:** they increase the neuromuscular blockade of competitive blockers.

**B. Depolarizing agents:**
They work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh. However, these agents are more resistant to degradation by acetylcholinesterase.

**Succinylcholine** is the only depolarizing muscle relaxant in use today.

1- mechanism of action:
succinylcholine attaches to the nicotinic receptor and acts like ACh to depolarize the junction. Unlike ACh, which is instantly destroyed by AChE, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively longer time and providing constant stimulation of the receptor.

# the duration of action of succinylcholine is dependent on diffusion from the motor endplate and hydrolysis by plasma pseudochochinesterase.
# low levels of pseudochochinesterase or absent of it in plasma leads to prolonged neuromuscular paralysis.

2- Actions:
succinylcholine initially produces brief muscle fasciculations (twitching of the muscle) that causes 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 pseudochochinesterase. However, succinylcholine that gets to the NMJ is not metabolized by AChE. (therapeutic effect only lasts a few minutes)

3- therapeutic use:
Because of its rapid onset of action, succinylcholine is useful when rapid endotracheal intubation is required during the induction of anesthesia, it is also used during electroconvulsivve shock treatment.

4- Pharmacokinetics:
Succinylcholine is injected intravenously, its brief duration of action results from redistribution and rapid hydrolysis by plasma pseudochochinesterase. Therefore, it is sometimes given by continuous infusion to maintain a longer duration of effect. (drug effect rapidly disappear upon discontinuation)

5- adverse effects:

a- hyperthermia: succinylcholine can potentially induce malignant hyperthermia in susceptible patients.

b- Apnea: administration of succinylcholine to a patient who is deficient in plasma cholinesterase or 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 who receive this drug or receiving digoxin and diuretics (electrolyte imbalances).

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.