



Drugs Affecting the Autonomic Nervous System-3

Cholinergic Antagonists

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- The cholinergic antagonists (also called cholinergic blockers, parasympatholytics or anticholinergic drugs)
- Bind to cholinergic receptors, but they do not trigger the usual receptor-mediated intracellular effects.
- The most useful of these agents selectively block muscarinic synapses of the parasympathetic nerves

Cholinergic antagonist classified into:

- Antimuscarinic Agents:
 - M1 Selective.
 - Non selective.
- Antinicotinic Agents:
 - Ganglionic Blocking Agents.
 - Neuromuscular Blocking Agents.

Antimuscarinic Agents

➤ Tertiary amine

(Alkaloid esters of tropic acid)

- Atropine: (prototype)
- Hemoatropine:
- Scopolamine.

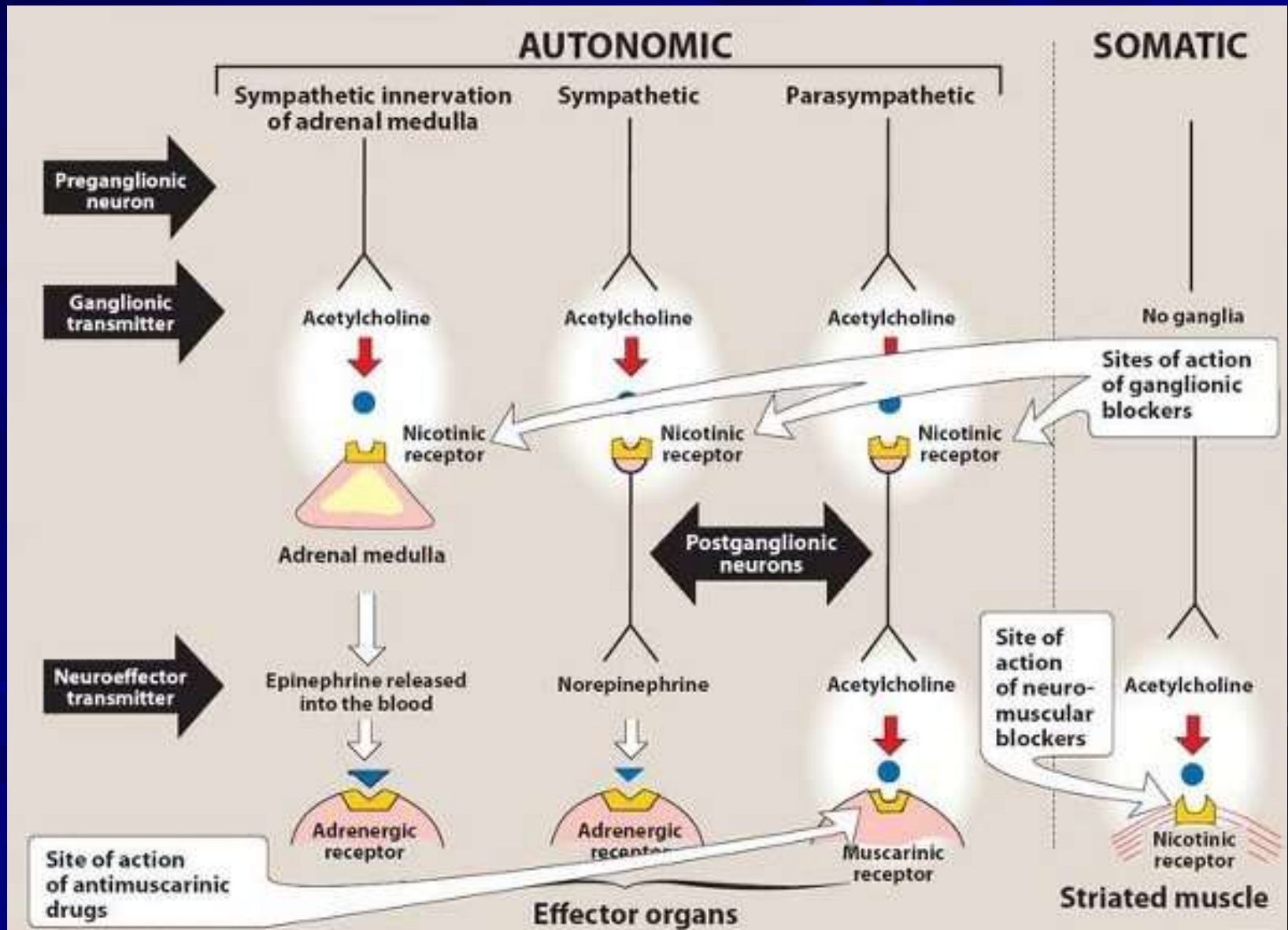
➤ Quaternary amine

(Semi synthetic & synthetic)

Produce more peripheral effects with decrease CNS effect.

- Propantheline
- Ipratropium
- Clidinium bromide.

Sites of Actions of Cholinergic Antagonists



Antimuscarinic Agents

Tertiary amine

Atropine

- A tertiary amine belladonna alkaloid
- Acts both centrally and peripherally
- It has a high affinity for muscarinic receptors, binds competitively & reversibly, preventing Ach from binding to that site.
- Block muscarinic receptors causing inhibition of all muscarinic functions.
- Block the few exceptional sympathetic neurons that are cholinergic, such as those innervating salivary and sweat glands.

- Have little or no action at skeletal neuromuscular junctions or autonomic ganglia (because they do not block nicotinic receptors).
- Its general actions last about 4 hours except when placed topically in the eye, where the action may last for days

Note: A number of antihistaminic and antidepressant drugs also have antimuscarinic activity.

Actions

Eye

- Dilates the pupil (mydriasis).
- Cycloplegia ,Light enter freely and the normal pupillary reflex accommodation is paralyzed (cycloplegia) and the lens is fixed for far vision.
- Increase intraocular pressure
- Decrease lachrymal secretion (sandy eyes)

Gastrointestinal (GI)

- Atropine and scopolamine can be used as an antispasmodic to reduce activity of the GI tract.
- The drug is not effective in promoting healing of peptic ulcer hydrochloric acid production (is not significantly affected).

Urinary system

- Atropine reduce hypermotility states of the urinary bladder. It is still occasionally used in enuresis (involuntary voiding of urine) among children

Note: α -adrenergic agonists with fewer side effects may be more effective

Respiratory

- Bronchial dilatation
- Decrease secretion

Cardiovascular

- Atropine block the cardiac receptors on the SA node so the cardiac rate increases modestly (tachycardia).
- It has no significant effect on peripheral blood vessels in therapeutic dose but with poisoning, there is marked vasodilatation

Secretions

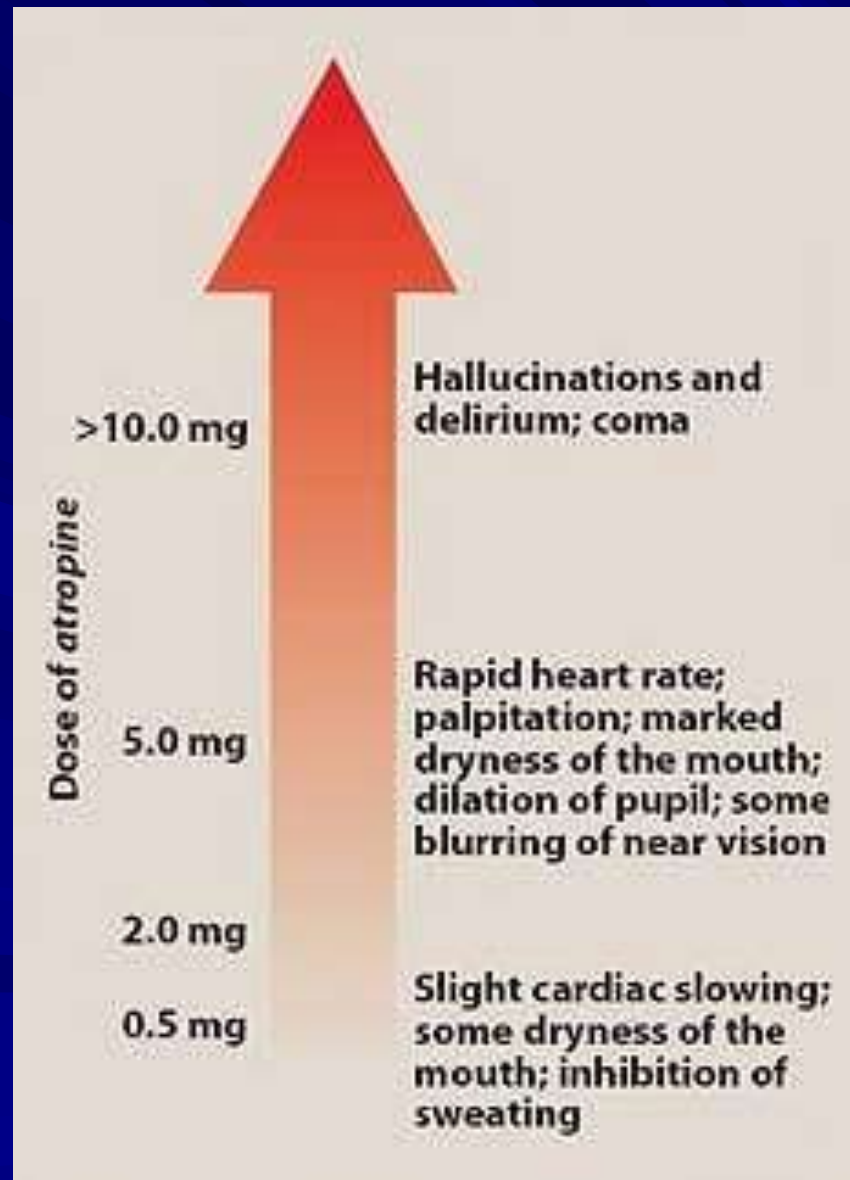
- Atropine blocks the salivary glands, producing a drying effect on the oral mucous membranes (xerostomia).
- Sweat and lacrimal glands are also affected.

Note: Inhibition of secretions by sweat glands can cause elevated body temperature.

CNS

- Has minimal stimulant effect (at normal dose) and slow sedation

Dose-dependent effects of atropine



Pharmacokinetics of Atropine

- It is readily absorbed
- Partially metabolized by the liver, and eliminated primarily in the urine
- It has a half-life of about 4 hours.

Adverse Effects (Depending on the dose)

- Dry mouth
- Blurred vision
- Sandy eyes
- Tachycardia
- Constipation
- CNS : restlessness, confusion, hallucinations, and delirium, depression
- Collapse of the circulatory and respiratory systems, and death.

- In older individuals, the use of atropine to induce mydriasis and cycloplegia may cause glaucoma.
- In other older individuals, atropine may induce urinary retention
- Children atropine, cause rapid increases in body temperature.

Note: Low doses of cholinesterase inhibitors such as physostigmine may be used to overcome atropine toxicity

Hemoatropine: Semi synthetic

Scopolamine:

- Tertiary amine belladonna alkaloid
- Produces peripheral effects similar to those of atropine
- Scopolamine has greater action on the CNS (unlike with atropine, CNS effects are observed at therapeutic doses)
- Longer duration of action than atropine

Clinical uses of antimuscarinic agents:

Ophthalmic

- (Atropine (hyoscyamine), Homotropine): used in cases that need mydriasis with cycloplagia (prolonged action).
Shorter-acting antimuscarinics (cyclopentolante and tropicamide) have largely replaced atropine due to prolonged mydriasis observed with atropine (7-14 days versus 6-24 hours with other agents).
- Antispasmodic: Atropine is used as an antispasmodic agent to relax the GI tract and bladder.

Antidote for cholinergic agonists

- Atropine is used for the treatment of overdoses of cholinesterase inhibitor insecticides and some types of mushroom poisoning
- The ability of atropine to enter the central nervous system (CNS) is of particular importance.

Central nervous system disorder

Parkinson's disease

- A number of centrally acting antimuscarinic preparations may improve the tremor and rigidity of parkinsonism but have little effect on bradykinesia. Orpheradrine, Benztropine mesylate

Prevent or reduce motion sickness

- Scopolamine for seasickness ,It can be given by injection, by mouth, or as a transdermal patch. The patch formulation produces significant blood levels over 48-72 hours

Respiratory disorder

- Ipratropium ,**tiotropium**(inhaled)for asthma and COPD in patients unable to take adrenergic.
- Tiotropium has a longer bronchodilator action and can be given once daily
- Pre anesthetic injection of Atropine or Scopolamine decrease bronchial secretion ,
- Scopolamine cause amnesia for events associated with surgery.

GIT

- Propantheline for irritable bowel syndrome, cause relaxation of smooth muscle (antispasmodic)
- Hyosine butyl bromide (Buscopan): relaxant of the smooth muscle
- Scopolamine (hyoscine), promethazine: used as antiemetic.
- Peptic ulcer: M1 inhibitor (Pirenzepine)
- Clidinium bromide: for gastric disorders, sometimes combine with chlordiazepoxide (called librax).

Urinary Disorders

- Atropine and other antimuscarinic drugs used to provide symptomatic relief in the treatment of urinary urgency caused by minor inflammatory bladder disorders. Oxybutynin, selective for M_3 receptors, is used to relieve bladder spasm after urologic surgery, eg, prostatectomy

Summary of cholinergic antagonists

	Drug	Therapeutic uses
Muscarinic blockers	<i>Cyclopentolate</i> <i>Tropicamide</i> <i>Atropine*</i>	In ophthalmology, to produce mydriasis and cycloplegia prior to refraction
	<i>Atropine*</i>	To treat spastic disorders of the GI and lower urinary tract To treat organophosphate poisoning To suppress respiratory secretions prior to surgery
	<i>Scopolamine</i>	In obstetrics, with morphine to produce amnesia and sedation To prevent motion sickness
	<i>Ipratropium</i>	Treatment of asthma
Ganglionic blockers	<i>Nicotine</i>	None
	<i>Mecamylamine</i>	Treatment of moderate to severe hypertension

Ganglionic Blockers:

- Competitively block the action of acetylcholine and similar agonists at nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia.
- Some members of the group also block the ion channel that is gated by the nicotinic cholinergic receptor.
- They have limited clinical use (due to lack of selectivity) but used in pharmacologic and physiologic research

- Ganglionic nicotinic receptors, depolarizing and nondepolarizing blockade
- Drugs now used as ganglion blockers are classified as nondepolarizing competitive antagonists.

Nicotine:

- Nicotine is available as patches, lozenges, gums, and other forms. Patches are available for application to the skin.
- The drug is absorbed and is effective in reducing the craving for nicotine in people who wish to stop smoking.

Mecamylamine:

- Competitive nicotinic blockade of the ganglia.
- Good oral absorption
- Duration of action is about 10 hours after a single administration.

Trimethaphan

- It is the only Ganglion-blocker still in clinical use.
- Its poorly lipid soluble.
- Short-acting ganglion blocker
- Inactive orally and is given by intravenous infusion.
- Used to lower blood pressure in emergency situations (malignant hypertension).

Hexamethonium

For management of hypertension

Neuromuscular Blockers

- These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the neuromuscular end plate of skeletal muscle

Nondepolarizing (competitive) blockers

Tubocurarine (prototype agent)

- It has been largely replaced by other agents due to side effects
- 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.

Note: Higher doses of anesthesia may produce respiratory paralysis and cardiac depression, increasing recovery time after surgery.

Mechanism of action:

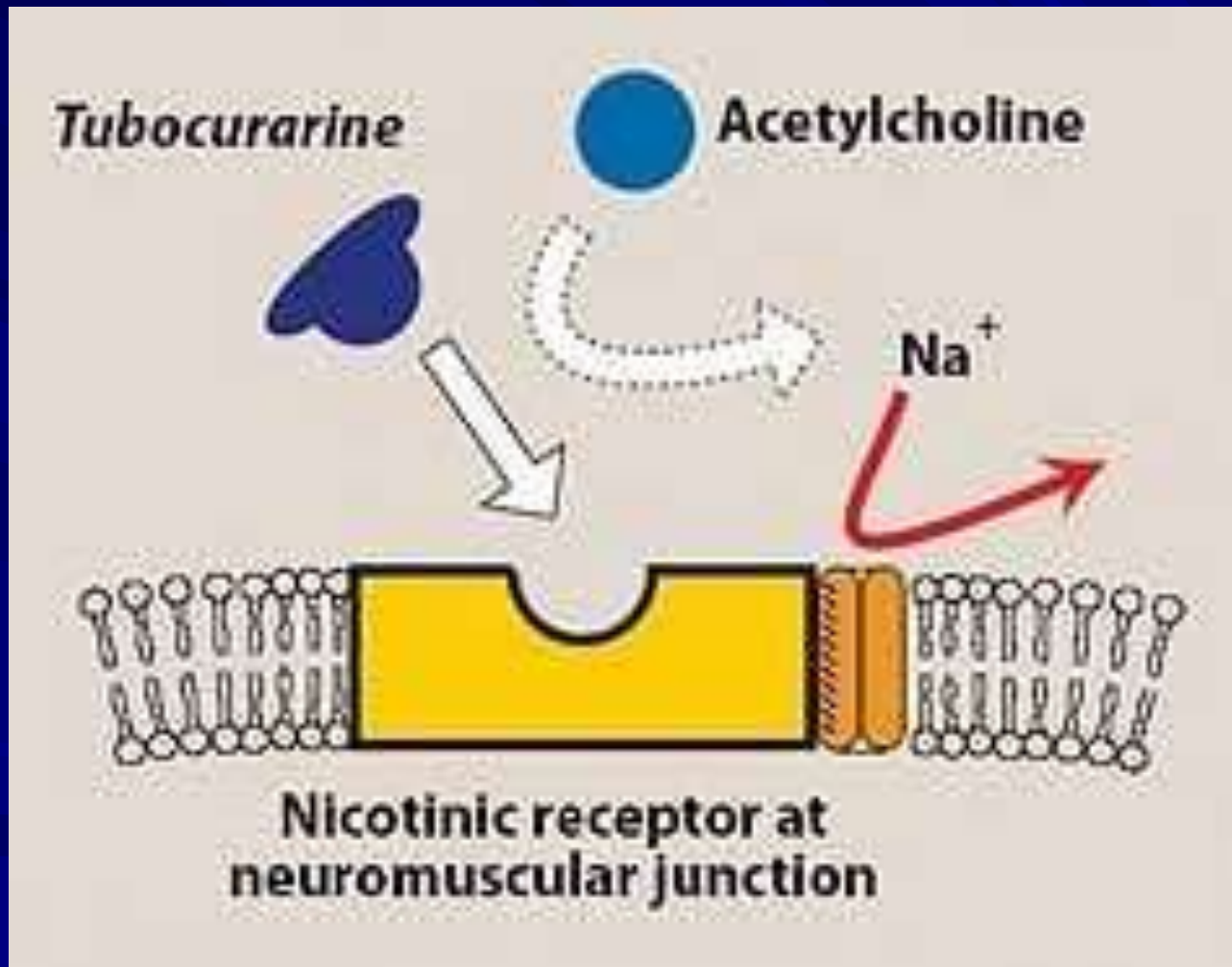
At low doses:

- Nondepolarizing neuromuscular blocking drugs (competitive blockers) interact with the nicotinic receptors to prevent the binding of acetylcholine (prevent depolarization of the muscle cell membrane and inhibit muscular contraction)
- Their action can be overcome by administration of cholinesterase inhibitors, Anesthesiologists often employ this strategy to shorten the duration of the neuromuscular blockade.

At High Doses:

Nondepolarizing blockers can block the ion channels of the end plate. This leads to further weakening of neuromuscular transmission, and it reduces the ability of acetylcholinesterase inhibitors to reverse the actions of nondepolarizing muscle relaxants.

Mechanism of action of competitive neuromuscular blocking drugs.



Therapeutic Uses: In Anesthesia

- Facilitate intubation
- Relax skeletal muscle during surgery.
- Orthopedic surgery

Pharmacokinetics:

- Injected intravenously, (oral absorption is minimal)
- Most non depolarizing agents have relatively long half life ranging from (20 min - several hours).
- Not enter cells or cross the blood-brain barrier.
- Many of the drugs are not metabolized.
- Most drug (tubocurarine, pancuronium, mivacurium, metocurine) are excreted in the urine unchanged

Pharmacokinetics of the neuromuscular blocking drugs



Drug Interactions:

- Cholinesterase inhibitors
- Halogenated hydrocarbon anesthetics (halothane) act to enhance neuromuscular blockade by exerting a stabilizing action at the neuromuscular junction.
- Aminoglycoside antibiotics (gentamicin or tobramycin)inhibit acetylcholine release from cholinergic nerves by competing with calcium ions. They synergize with tubocurarine and other competitive blockers, enhancing the blockade.
- Calcium-channel blockers: These agents may increase the neuromuscular block of tubocurarine and other competitive blockers as well as depolarizing blockers.

Depolarizing Agents

Mechanism of Action:

Succinylcholine attaches to the nicotinic receptor and acts like acetylcholine to depolarize the junction. Unlike acetylcholine, which is destroyed by acetylcholinesterase, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively longer time and providing a constant stimulation of the receptor.

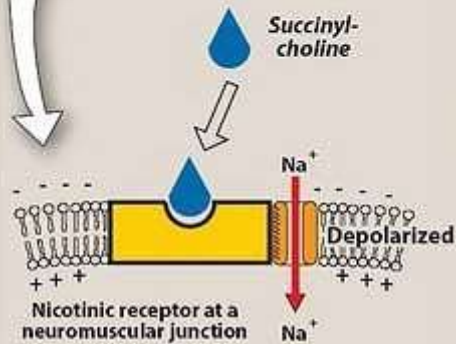
Therapeutic Uses:

- Because of its rapid onset and short duration of action (total paralysis last up to 4 min)
- 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 employed during electroconvulsive shock treatment.

Mechanism of action of depolarizing neuromuscular blocking drugs

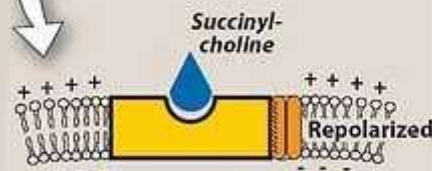
PHASE I

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.



Pharmacokinetics:

- Succinylcholine is injected intravenously.
- Its brief duration of action (several minutes) results from redistribution and rapid hydrolysis by plasma cholinesterase. It therefore is usually given by continuous infusion

Adverse Effect

1. Malignant Hyperthermia

- When halothane is used as an anesthetic, administration of succinylcholine has occasionally caused malignant hyperthermia (with muscular rigidity and hyperpyrexia) in genetically susceptible people. This is treated by rapidly cooling the patient and by administration of dantrolene, which blocks release of Ca^{2+} from the sarcoplasmic reticulum of muscle cells, thus reducing heat production and relaxing muscle tone.

2. Apnea

- Administration of succinylcholine to a patient who is genetically deficient in plasma cholinesterase or has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm.

3. Hyperkalemia

- Succinylcholine increases potassium release from intracellular stores. This may be particularly dangerous in burn patients or patients with massive tissue damage in which potassium is being rapidly lost from cells.