

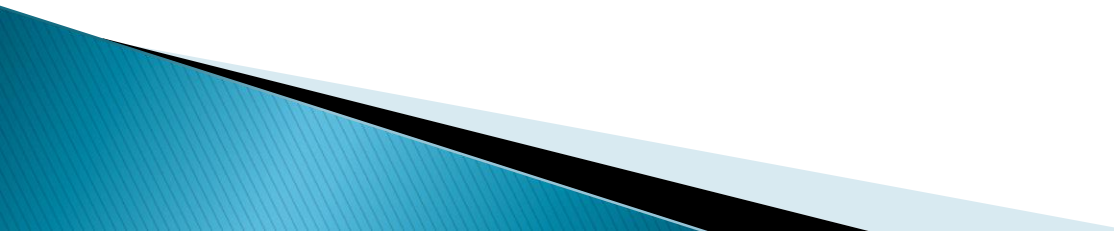
Skeletal muscle relaxants

Prof. Hanan Hagar



Learning objectives

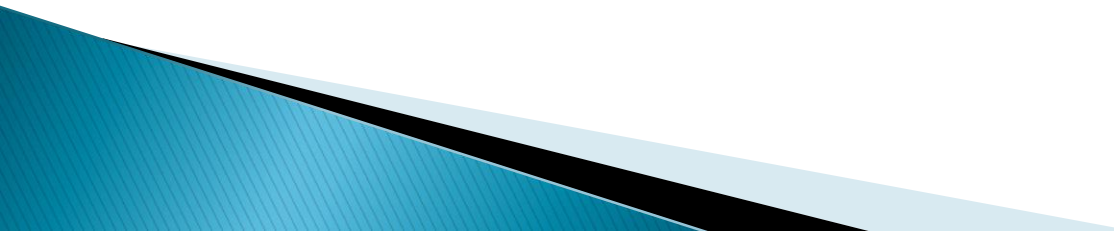
By the end of this lecture, students should be able to:

- **Identify classification of skeletal muscle relaxants**
 - **Describe the pharmacokinetics and dynamics of neuromuscular relaxants**
 - **Recognize the clinical applications for neuromuscular blockers**
 - **Know the different types of spasmolytics**
 - **Describe the pharmacokinetics and dynamics of spasmolytic drugs**
 - **Recognize the clinical applications for spasmolytic drugs**
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Skeletal muscle relaxants

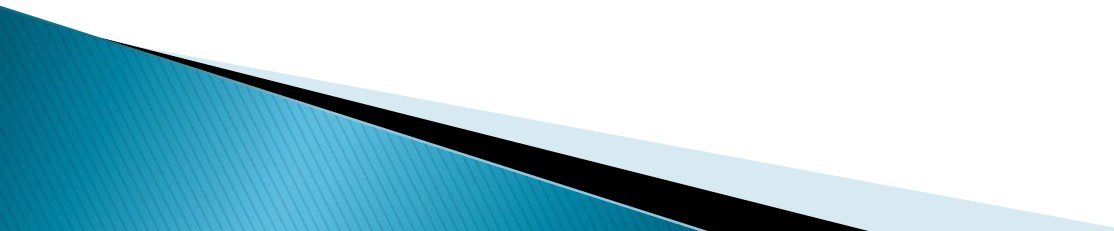
Are drugs used to induce skeletal muscle relaxation.

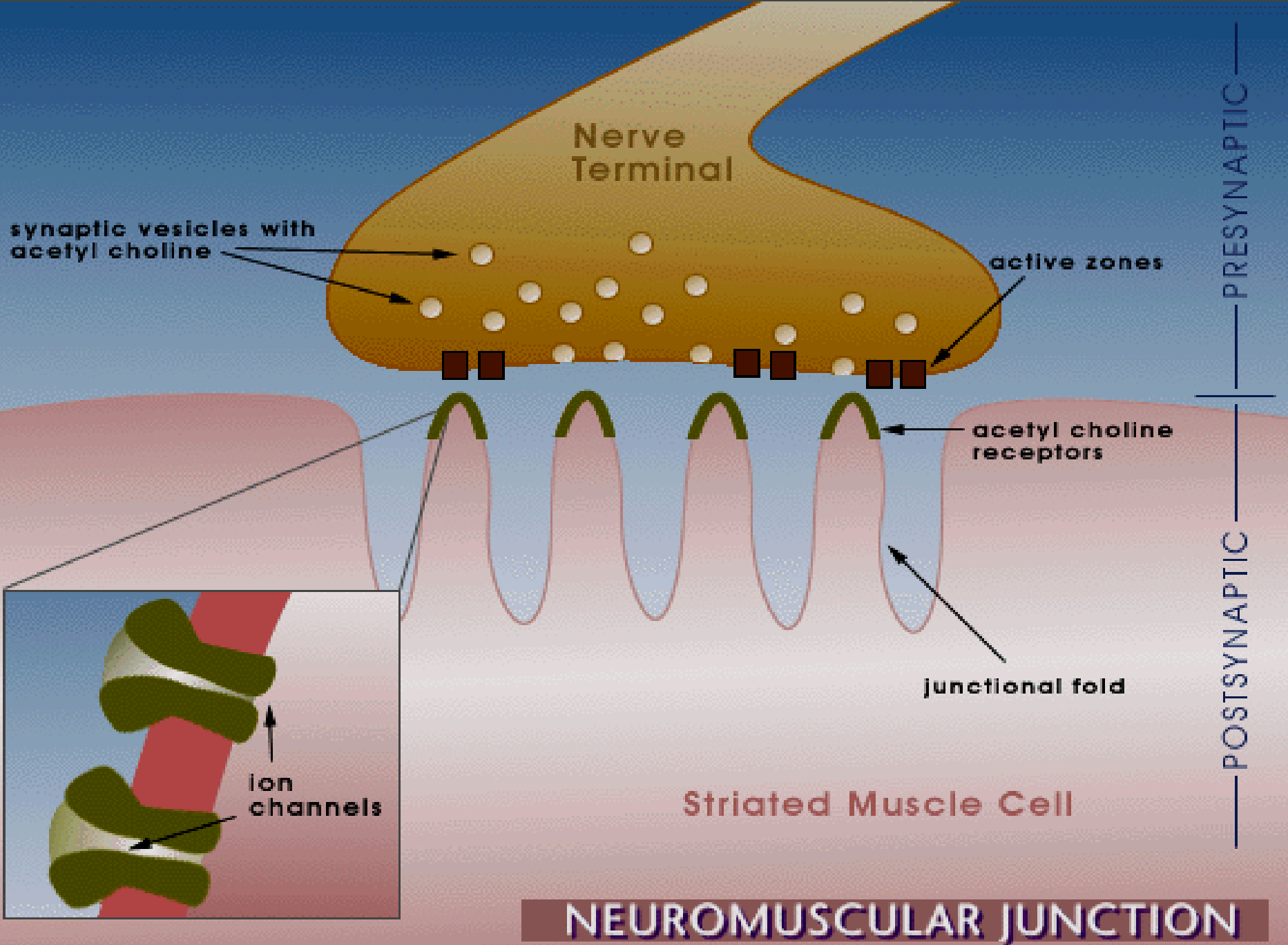
Classification of SKM relaxants

- **Peripherally acting skeletal muscle relaxants**
 - **Centrally acting skeletal muscle relaxants e.g.**
Baclofen – Diazepam
 - **Direct acting skeletal muscle relaxants e.g.**
Dantrolene
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Peripherally acting SKM relaxants (Neuromuscular blockers)

Neuromuscular blockers act by blocking neuromuscular junction or motor end plate leading to skeletal muscle relaxation.





synaptic vesicles with acetyl choline

Nerve Terminal

active zones

acetyl choline receptors

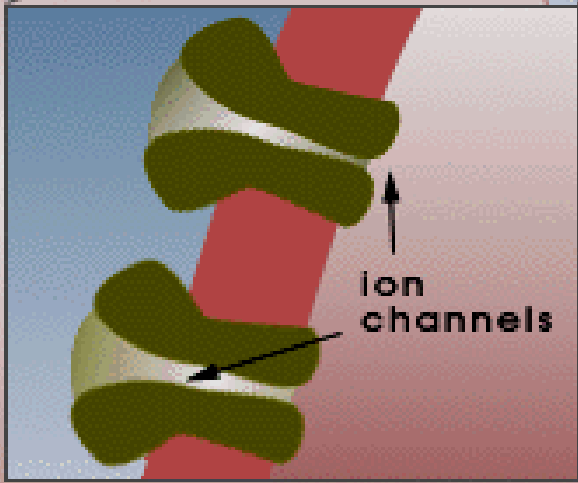
junctional fold

Striated Muscle Cell

PRESYNAPTIC

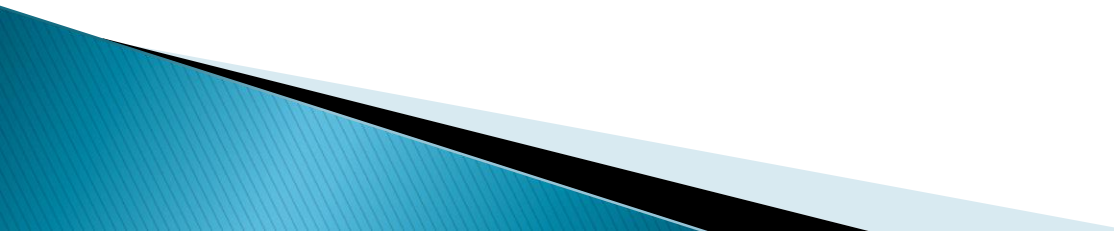
POSTSYNAPTIC

NEUROMUSCULAR JUNCTION



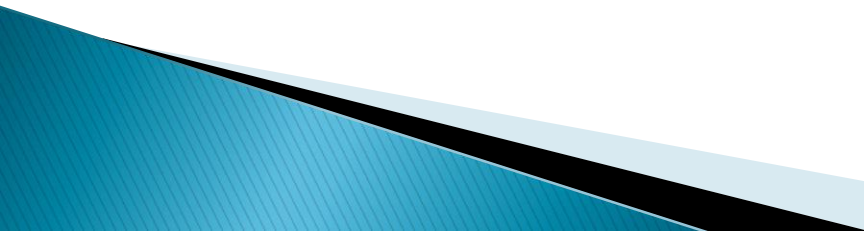
Classification of Peripherally SKM relaxants

According to mechanism of action, they are classified into:

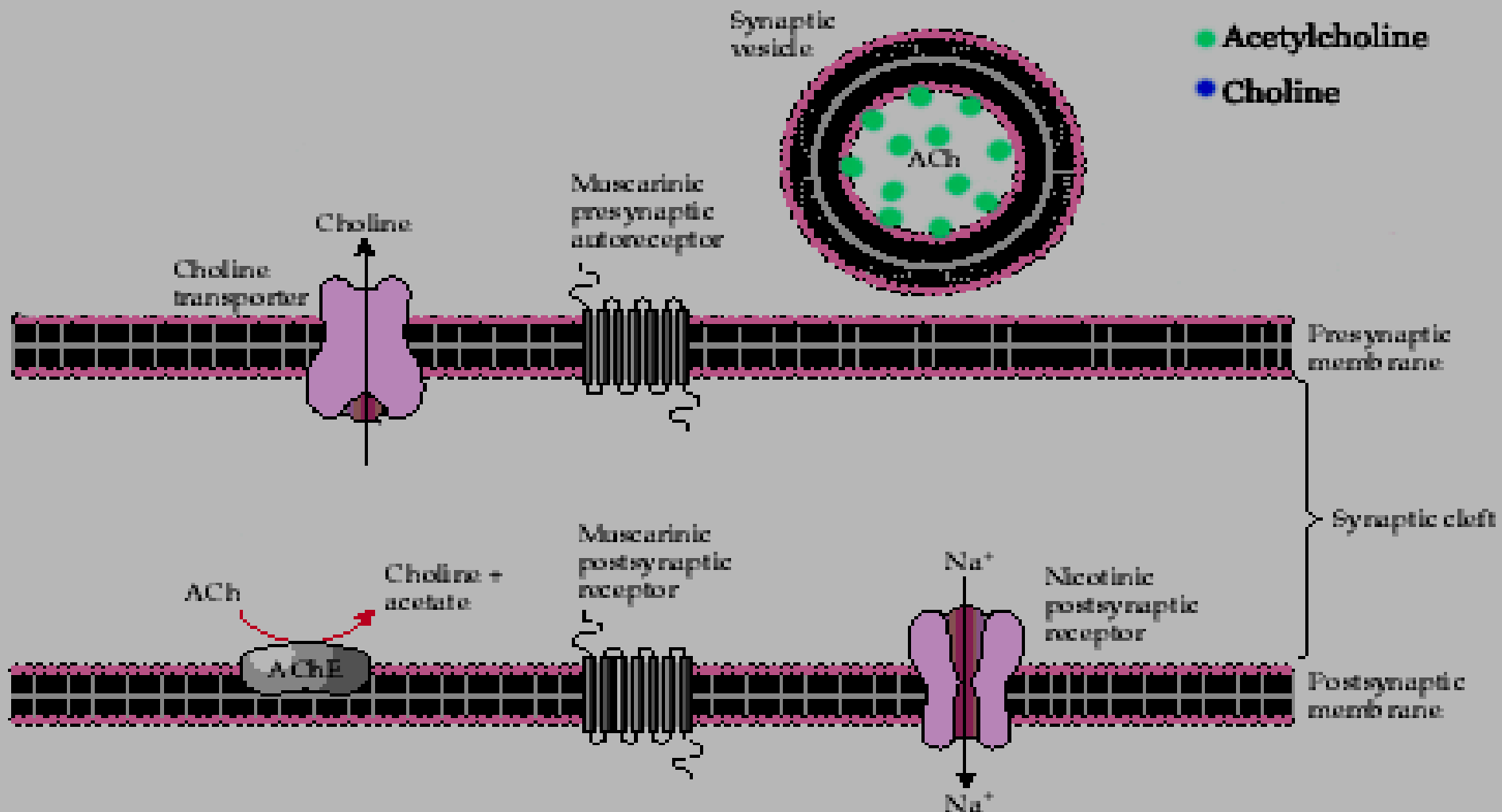
- 1. Competitive neuromuscular blockers**
 - 2. Depolarizing neuromuscular blockers**
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Competitive neuromuscular blockers

Mechanism of action:

- ▶ Compete with **Ach** for the **nicotinic receptors** present in postjunctional membrane of neuromuscular junction or motor end plate.
 - ▶ No depolarization of postjunctional membrane (non depolarizing).
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Neuromuscular Junction



Competitive neuromuscular blockers

Have the common suffix **curium** or **curonium**

Classified according to duration of action into:

- ✓ Atracurium
- ✓ Mivacurium
- ✓ Pancuronium
- ✓ Vecuronium

Competitive Neuromuscular Blockers

▶ Long acting

- **d-tubocurarine** (prototype drug)
- Pancuronium

▶ Intermediate acting

- Atracurium Vecuronium

▶ Short acting

- Mivacurium

Pharmacokinetics of competitive neuromuscular blockers:

- They are **polar compounds**
 - Inactive orally & taken parentally
 - Do not cross BBB (no central action)
 - Do not cross placenta
- Metabolism depend upon kidney or liver

Except

Mivacurium (degraded by acetyl cholinesterase)

Atracurium (spontaneous degradation in blood)

Pharmacological actions of competitive NMBs:

- ▶ Skeletal muscle relaxation.
- ▶ They produce different effects on CVS
- ▶ Some release histamine and produce hypotension
 - d-Tubocurarine
 - Atracurium
 - Mivacurium
- ▶ Others produce tachycardia (↑ H.R)
 - Pancuronium


d – Tubocurarine

- Long duration of action (1 - 2 h)
- Eliminated by kidney 60% - liver 40%.
- Not used clinically due to adverse effects:
 - Histamine releaser leading to
 - Bronchospasm (constriction of bronchial smooth muscles).
 - Hypotension
 - Tachycardia
- More safer derivatives are now available

Atracurium

- ▶ As potent as curare
- ▶ Has intermediate duration of action (30 min).
- ▶ Liberate histamine → (Transient hypotension)
- ▶ Eliminated by non enzymatic chemical degradation in plasma (*spontaneous hydrolysis at body pH*).
- ▶ used in liver failure & kidney failure (*drug of choice*).
- ▶ Should be avoided in asthmatic patients **Why?**

Mivacurium

- ▶ Chemically related to atracurium
 - ▶ Fast onset of action
 - ▶ Has the shortest duration of action (15 min) of all competitive neuromuscular blockers.
 - ▶ Metabolized by pseudo-cholinesterase.
 - ▶ **Longer** duration in patient with liver disease or genetic **cholinesterase deficiency** or **malnutrition**.
 - ▶ Transient hypotension (due to histamine release).
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Pancuronium

- ▶ More potent than curare (6 times).
- ▶ Excreted by the kidney (80 %).
- ▶ Long duration of action.

Side effects:

- ▶ Hypertension, tachycardia
 - ▶ ↑ norepinephrine release from adrenergic nerve endings
 - ▶ Antimuscarinic action (**block parasympathetic action**).
 - Avoid in patient with coronary diseases.

Vecuronium

- More potent than tubocurarine (6 times).
- Metabolized mainly by liver and excreted in bile.
- Intermediate duration of action.
- Has few side effects.
 - No histamine release.
 - No tachycardia.

Depolarizing Neuromuscular Blockers

Mechanism of action

- ▶ combine with nicotinic receptors in post-junctional membrane of neuromuscular junction → **initial** depolarization of motor end plate → muscle twitching → **persistent** depolarization → **SKM relaxation**

Succinylcholine (suxamethonium)

Pharmacological Actions

Skeletal muscles: twitching → relaxation

Hyperkalemia: Cardiac arrest.

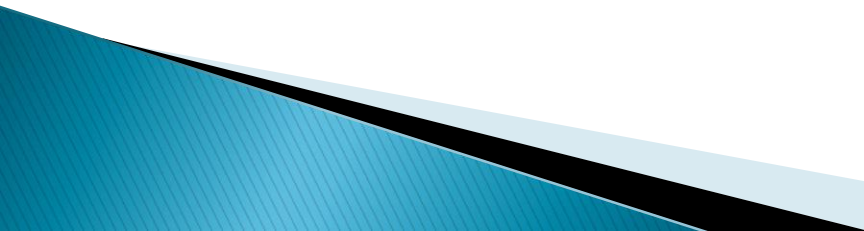
CVS: arrhythmia

Eye: ↑ intraocular pressure (due to contraction of extra-ocular muscle).

Pharmacokinetics

- ▶ Fast onset of action (1 min.).
- ▶ Short duration of action (5-10 min.).
- ▶ Metabolized by pseudo-cholinesterase in plasma
- ▶ Half life is prolonged in
 - Neonates
 - Elderly
 - Pseudo-cholinesterase deficiency (liver disease or malnutrition or genetic cholinesterase deficiency).

Side Effects

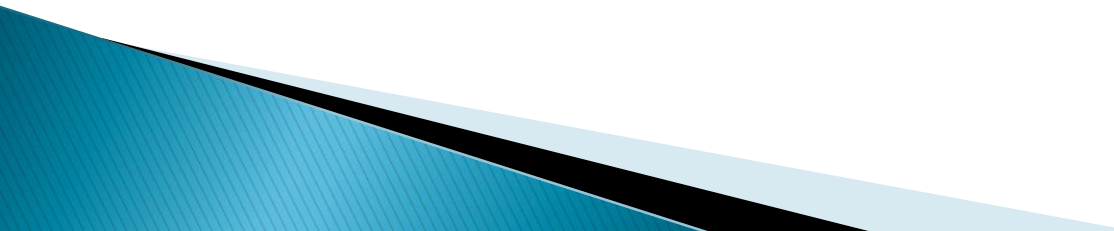
- ▶ Hyperkalemia
 - ▶ CVS arrhythmia
 - ▶ ↑ Intraocular pressure contraindicated in **glaucoma**
 - ▶ Can produce **malignant hyperthermia**
 - ▶ May cause **succinylcholine apnea** due to deficiency of pseudo-cholinesterase.
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Malignant Hyperthermia

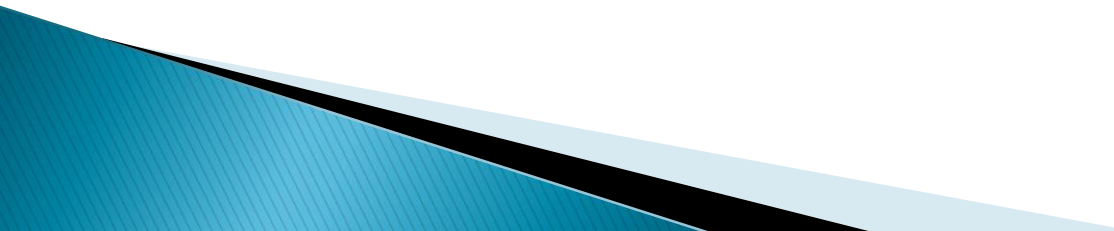
- ▶ Is a rare **inherited** condition that occurs upon administration of drugs as:
 - general anesthesia e.g. halothane
 - neuromuscular blockers e.g. succinylcholine
- ▶ Inability to bind calcium by sarcoplasmic reticulum in some patients due to genetic defect.
- ▶ ↑ Ca release, intense muscle spasm, hyperthermia

<i>Drug</i>	<i>Duration</i>	<i>Side effects</i>	<i>Notes</i>
Tubocurarine	Long 1-2 h	Hypotension	# Renal failure
Pancuronium	Long 1-2 h	Tachycardia	# Renal failure
Atracurium	Short 30 min.	Transient hypotension Histamine release	Spontaneous degradation Used in liver and kidney failure
Vecuronium	Short 40 min.	Few side effects	# Liver failure
Mivacurium	Short 15 min.	Similar to atracurium	Metabolized by pseudocholinesterase # Choline esterase deficiency
Succinyl choline	Short 10 min.	Hyperkalemia Arrhythmia Increase IOP	# CVS Diseases # Glaucoma # Liver disease

Uses of neuromuscular blockers

- ▶ control convulsion → electroshock therapy in psychotic patients.
 - ▶ Relieve of tetanus and epileptic convulsion.
 - ▶ As adjuvant in general anesthesia to induce muscle relaxation
 - ▶ Facilitate endotracheal intubation
 - ▶ Orthopedic surgery.
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Drugs and diseases that modify effects of neuromuscular blockers

- ▶ **Myasthenia gravis** increase the response to muscle relaxants.
 - ▶ **Drugs** as aminoglycosides (e.g. streptomycin), magnesium sulphate, general anesthetics can potentiate or enhance the effect of neuromuscular blockers.
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Spasmolytics

They reduce muscle spasm in spastic states

Baclofen:

- ▶ Centrally acting
- ▶ GABA agonist – acts on spinal cord.

Diazepam (Benzodiazepines):

- ▶ Centrally acting
- ▶ facilitate GABA action on CNS.

Dantrolene:

- ▶ direct action on skeletal muscles.

Dantrolene

Mechanism of action

- ▶ Acts directly on skeletal muscles.
- ▶ It interferes with the release of calcium from its stores in skeletal muscles (**sarcoplasmic reticulum**).
- ▶ It inhibits excitation-contraction coupling in the muscle fiber.
- ▶ Orally, IV, ($t_{1/2} = 8 - 9 \text{ h}$).
- ▶ **Used in the treatment of:**
 - ▶ Spastic states
 - ▶ Malignant hyperthermia

Uses of spasmolytics

They reduce muscle spasm in spastic states produced by neurological disorders as:

- Spinal cord injury
 - Cerebral stroke
 - Cerebral palsy
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