SKELETAL MUSCLE RELAXANTS

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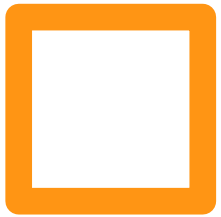
Introduction

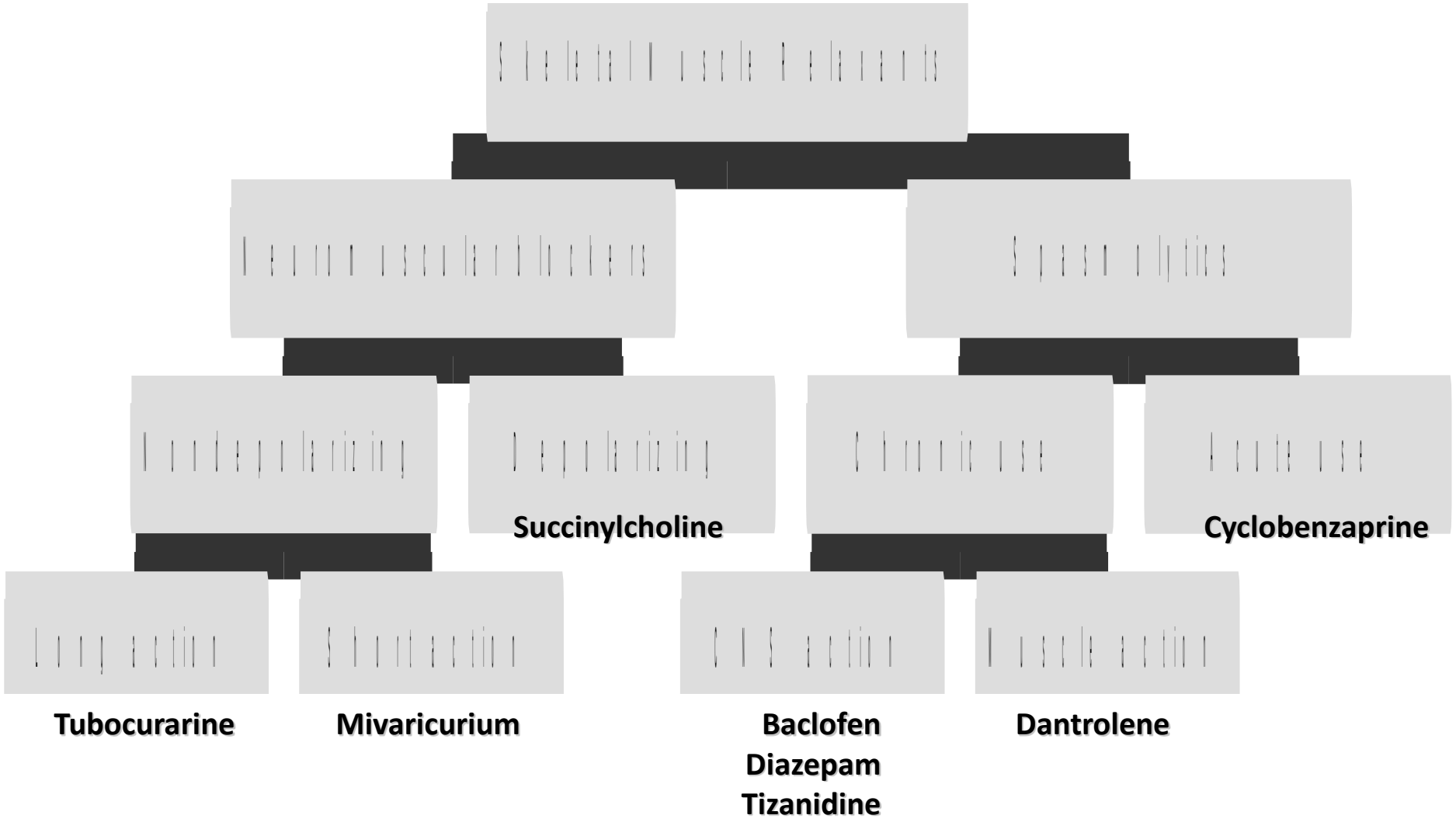
- A **muscle relaxant** is a drug that:
  - affects skeletal muscle function
  - decreases the muscle tone
- It may be used to alleviate symptoms such as muscle spasms and pain
- The term "muscle relaxant" is used to refer to two major therapeutic groups:
  - neuromuscular blockers
  - spasmolytics
- Both are grouped together as muscle relaxants; the term is commonly used to refer to spasmolytics only



Skeletal Muscle Relaxants

Divided into

- **Neuromuscular blocking agents**
  - Act at the skeletal myoneural junction
  - to produce muscle paralysis to facilitate
  - surgery or artificial ventilation
- **Spasmolytic drugs**
  - Act on the CNS to reduce abnormally
  - elevated tone caused by neurologic or
  - muscle endplate disease


Succinylcholine
Cyclobenzaprine
Tubocurarine
Mivaricurium
Baclofen
Diazepam
Tizanidine
Dantrolene

Muscle Relaxants function

- Relieve muscular spasms and pain associated with traumatic injuries and spasticity from chronic debilitating disorders
- Spasticity results from increased muscle tone from hyper excitable neurons caused by increased stimulation from the cerebral neurons or lack of inhibition in the spinal cord or at the skeletal muscles.

NEUROMUSCULAR BLOCKING DRUGS

A. Classification and prototypes

- Evoked by a nicotinic cholinergic transmission process
- Blockade of transmission at the skeletal muscle endplate (postsynaptic structure bearing the nicotinic receptors)
  - Produces relaxation of muscle
  - A requirement for surgery

NEUROMUSCULAR BLOCKING DRUGS

A. Quaternary amines

- Structurally related to acetylcholine (ACh)
  - **Nondepolarizing type**
    - Nicotinic antagonist
    - Tubocurarine
  - **Depolarizing type**
    - Nicotinic agonist
    - Succinylcholine

Neuromuscular blockers

- **Nondepolarizing type**
  - Subclassified depending on chemical structure

- A. **Isoquinoline** derivatives
  - Atra**curium** cisatra**curium**
  - Doxa**curium** meto**curine**
  - Miva**curium** tubo**curarine**

NEUROMUSCULAR BLOCKING DRUGS

- **B.** Steroid derivatives
  - Pancuro**nium**
  - Piperacuro**nium**
  - Rocuro**nium**
  - Vecuro**nium**

Nondepolarizing neuromuscular blocking drugs

Pharmacokinetics

- All drugs are given IV
- Drugs metabolized by plasma cholinesterase
  - Mivacurium (shortest duration of action)
- Drugs eliminated in the bile have shorter duration of action
  - Vecuronium

Nondepolarizing neuromuscular blocking drugs

Mechanism of action

- Prevent the action of ACh at the skeletal muscle endplate
- Compete with ACh at the receptor site
- Effect is reversed by cholinesterase inhibitors
- Act as surmountable blockers
    - Overcomed by increasing the amount of agonist

Depolarizing neuromuscular blocking drugs

Pharmacokinetics

- Succinylcholine
  - Composed of 2 ACh molecules
  - Metabolized by the plasma cholinesterase

(butyrylcholinesterase or pseudocholinesterase)

  - Duration of action of only a few minutes if given as a single dose
  - Blockade may be prolonged in patients with genetic variants of plasma cholinesterase
- Metabolizes the drug very slowly
- Not rapidly hydrolyzed by acetylcholinesterase

Reversal of blockade of Nondepolarizing blockers

- Reversed by increasing the concentration of normal transmitter at the receptors
- Administration of cholinesterase inhibitors
  - **Neostigmine** and **physostigmine**

SPASMOLYTIC DRUGS USES

- Painful spasms
- Chronic diseases of the CNS
  - Cerebral palsy
  - Multiple sclerosis
  - Stroke
- Acute injury
  - Inflammation of muscle

SPASMOLYTIC DRUGS

Treatment goal in both acute and chronic conditions

- Reduction of excessive skeletal muscle tone without reduction of strength
- Reduced spasm results in reduction of pain and improved mobility

SPASMOLYTIC DRUGS

Drugs for chronic spasm

Classification

- Do not resemble ACh in structure or effect
- Act in the CNS or in the skeletal muscle than in the neuromuscular endplate
- All given oral

SPASMOLYTIC DRUGS

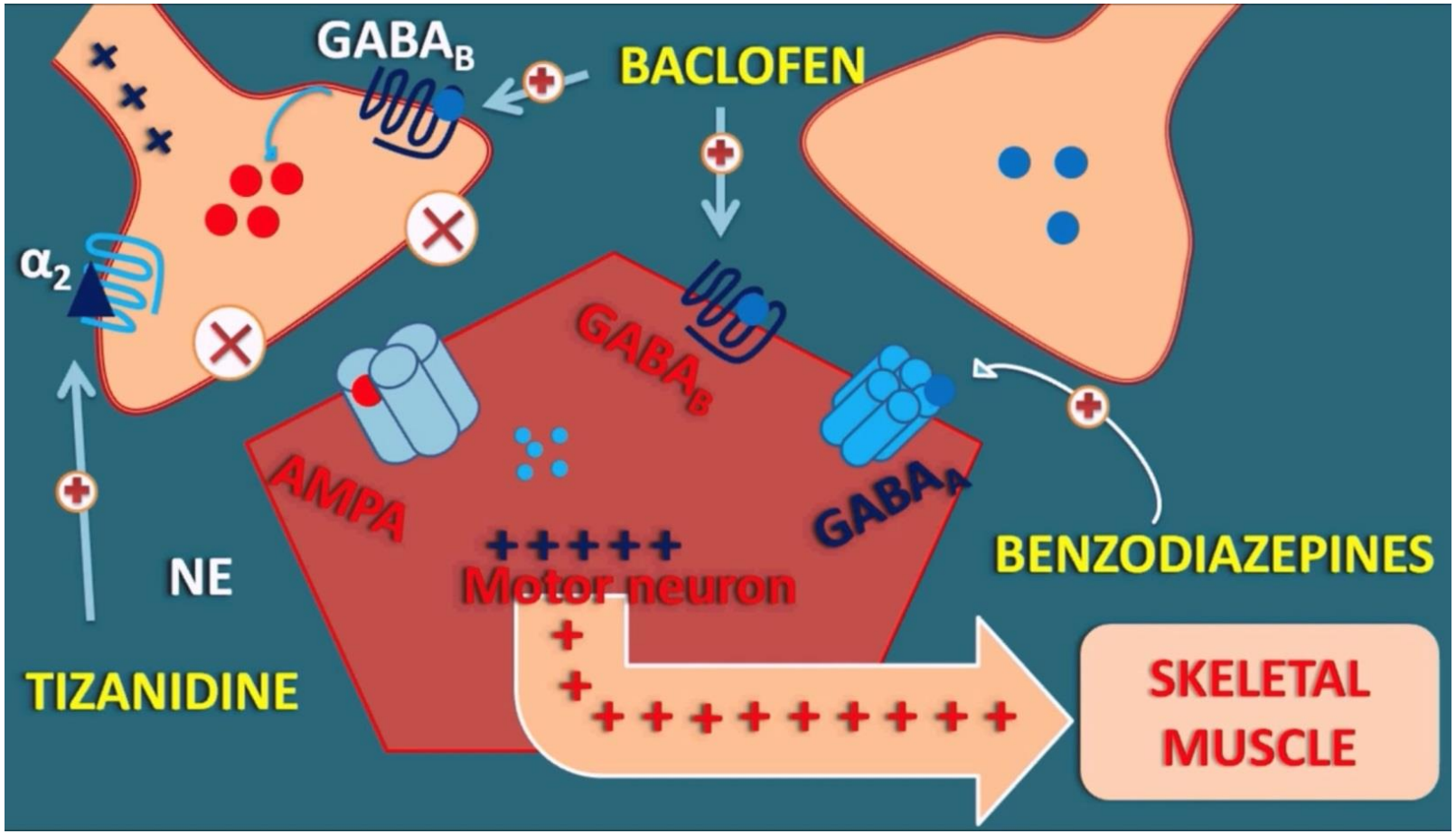
Classification and mechanisms of actions

- Diazepam
  - Benzodiazepine
  - Facilitates GABA-mediated presynaptic inhibition
- Baclofen
- GABA agonist causing membrane hyperpolarization
- Increased K^+ conductance
- Decreases the release of excitatory neurotransmitters including substance P

SPASMOLYTIC DRUGS

- Tizanidine
  - Imidazoline related to clonidine
  - With significant alpha$_2$ agonist activity
  - Reinforces both presynaptic and post-synaptic inhibition in the spinal cord

SPASMOLYTIC DRUGS



SPASMOLYTIC DRUGS

- Dantrolene
  - Acts on the sarcoplasmic reticulum of the skeletal muscle by reducing the release of activator Ca^{+2}
  - Used to treat and prevent Malignant hyperthermia
  - **Malignant hyperthermia** is
    - Massive release of Ca^{+2}
      - Uncontrolled contraction and
      - stimulation of metabolism in the
      - skeletal muscle
      - General anesthesia protocols with
      - succinylcholine and tubocurarine

SPASMOLYTIC DRUGS

Drugs for acute muscle spasm

- Promoted for treatment of acute spasm resulting from muscle injury
- Sedatives that act in the brain or spinal cord

SPASMOLYTIC DRUGS

- Cyclobenzaprine
  - Acts in the brain stem by interfering with the post synaptic reflexes that maintain skeletal muscle tone
  - Given oral
  - Marked sedative and muscarinic actions
  - May cause confusion, visual hallucinations
  - Not effective in muscle spasm resulting from cerebral palsy or spinal cord injury

- **CENTRAL ACTING MUSCLE RELAXANTS**
  - Are used in cases of spasticity to suppress hyperactive reflex and for muscle spasms that do not respond to anti-inflammatory agents, physical therapy or other forms of therapy.
  - Centrally acting muscle relaxants acts on the spinal cord.

- **SPASTICITY**
  - Is muscular hyperactivity that causes contractions of the muscles, resulting in pain and ,limited mobility.
  - Ex. Of centrally acting muscle relaxants that treat spasticity are **baclofen , dantrolene, and tizanidine.**
  - **Diazepam** a benzodiazepine has also been effective for treating spasticity

- **MUSCLE SPASMS**
  - Various centrally acting muscled relaxants are used for muscle spasms, to decrease pain and increase range of motion.
  - They have a sedative effect and should not be taken concurrently with CNS depressants such as barbiturates, narcotics, and alcohol
  - Dizziness and drowsiness are common side effects.
  - Examples of this group of centrally acting muscle relaxants are **carisoprodol, cyclobenzaprine, and methocarbamol**

Centrally Acting Muscle Relaxants

- **Carisprodol**
  - To relax skeletal muscles
  - Blocks interneuronal activity
  - Increase CNS depression with alcohol, narcotics, sedative-hypnotics, anti-histamines, tricyclic anti-depressants.
  - May increase risk for ventrivular fibrilation with calcium channel blockers.
  - Contraindicated with severe renal or renal disease.
  - Side effects are nausea, vomitting, dizziness, weakness, insomnia
  - Adverse reactions are asthmatic attack, tachycardia, hypotension, diplopia.

Summary-1

- Neuromuscular blockers act by interfering with transmission at the neuromuscular end
- They block neuromuscular transmission at the neuromuscular junction causing paralysis of the affected skeletal muscles
- They have no CNS activity
- Are used in surgical procedures to cause temporary paralysis
- They prevent spontaneous movement of muscle during surgical operations
- Quaternary ammonium muscle relaxants are quaternary ammonium salts used commonly in anesthesia
  - **Pancuronium** is the prototype drug
  - Others like vecuro**nium**, rocuro**nium**, rapacuro**nium**, dacuro**nium**, pipecuro**nium**, and chando**nium**

Summary-2

- Spasmolytics or "centrally acting muscle relaxants" are used to:
  - alleviate musculoskeletal pain and spasms
  - reduce spasticity in a variety of neurological conditions
  - affect CNS activity
- The term "spasmolytic" is also considered a synonym for antispasmodic
- Spasmolytics such as carisoprodol, methocarbamol, and metaxalone are commonly prescribed for low back pain or neck pain
- They are not:
  - recommended as first-line agents
  - more effective than paracetamol or (NSAIDs)
- Most spasmolytics have the side effects of:
  - sedation
  - drowsiness
  - dependence with long-term use

Thank you