Ganglion blocking agents

-*out of date*
-Specifically act on the nicotinic receptors of both parasymphatetic and sympathetic ganglia
- no selectivity toward PG or SG
-These drugs are non-depolarizing, competitive antagonists except nicotine
-Ganglionic blockade is rarely used therapeutically

Ganglionic Blocking Drugs

-used as antihypertensive agents in the past, limited use now
-have broad actions on sympathetic and parasympathetic systems
-have now been replaced by more selective antihypertensive drugs
-effects are:

•atony of the bladder and GI tract

•cycloplegia

•dry mouth

•orthostatic hypotension

•mild tachycardia and hypotension

eg. trimethaphan camsylate

Ganglionic blocking effects

Site	*Predominant tone*	*Effect of ganglionic block*
Arterioles	Sympathetic (adrenergic)	Vasodilation, ↑flow, hypotension
Veins	Sympathetic (adrenergic)	Dilation, pooling of blood, ↓preload, ↓cardiac output
Heart	Parasympathetic (cholinergic)	Tachycardia
Iris	Parasympathetic (cholinergic)	Mydriasis
Ciliary muscle	Parasympathetic (cholinergic)	Cycloplegia
GI tract	Parasympathetic (cholinergic)	↓Tone and motility, constipation

Ganglionic blocking effects (2)

Site	*Predominant tone*	*Effect of ganglionic block*
Urinary bladder	Parasympathetic (cholinergic)	Urinary retention
Salivary glands	Parasympathetic (cholinergic)	Xerostomia
Sweat glands	Sympathetic (cholinergic)	Anhidrosis

Ganglionic (Nn) blockers

- Trimethaphan
  - Intravenous drug
  - Hypertensive emergencies
  - Intraoperative blood pressure reduction
- Mecamylamine
  - Oral drug
  - Refractory hypertension
  - New interest in smoking cessation, mood disorders

- Nicotine

NEUROMUSCULAR BLOCKING AGENTS

Skeletal muscle relaxants act peripherally at neuromuscular junction. According to their action they are divided into the following groups.

- Nondepolarizing (competitive) agents or curare-like drugs
- Depolarizing agents

NEUROMUSCULAR BLOCKING AGENTS

(1) Nondepolarizing (competitive) agents

Long acting: d-Tubocurarine, Pancuronium, Doxacurium, Pipecuronium

Intermediate acting: Atracurium, Vecuronium

Short acting: Mivacurium

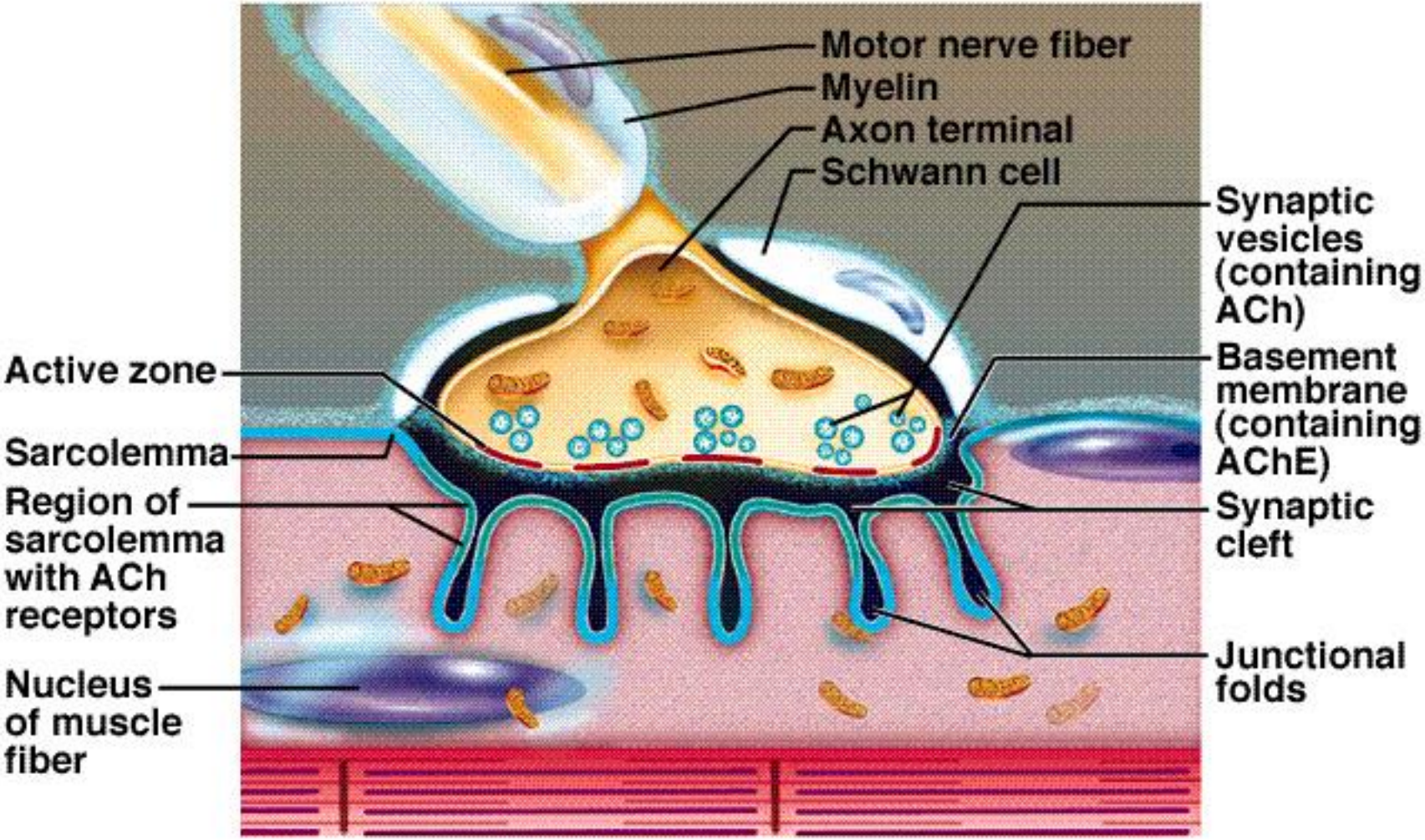
(2) Depolarizing agents

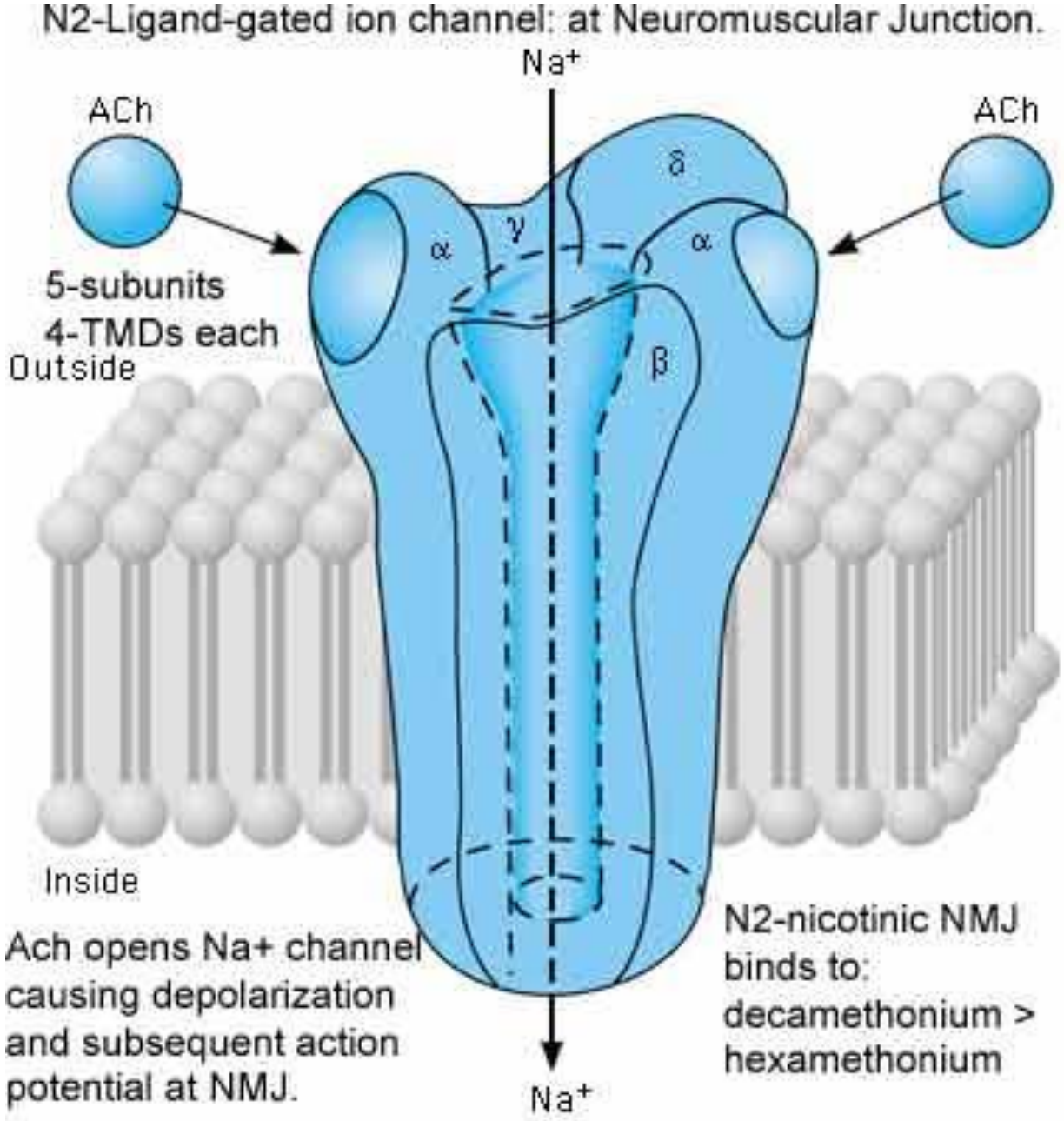
Suxamethonium (Succinylcholine)
Decamethonium (C-10)

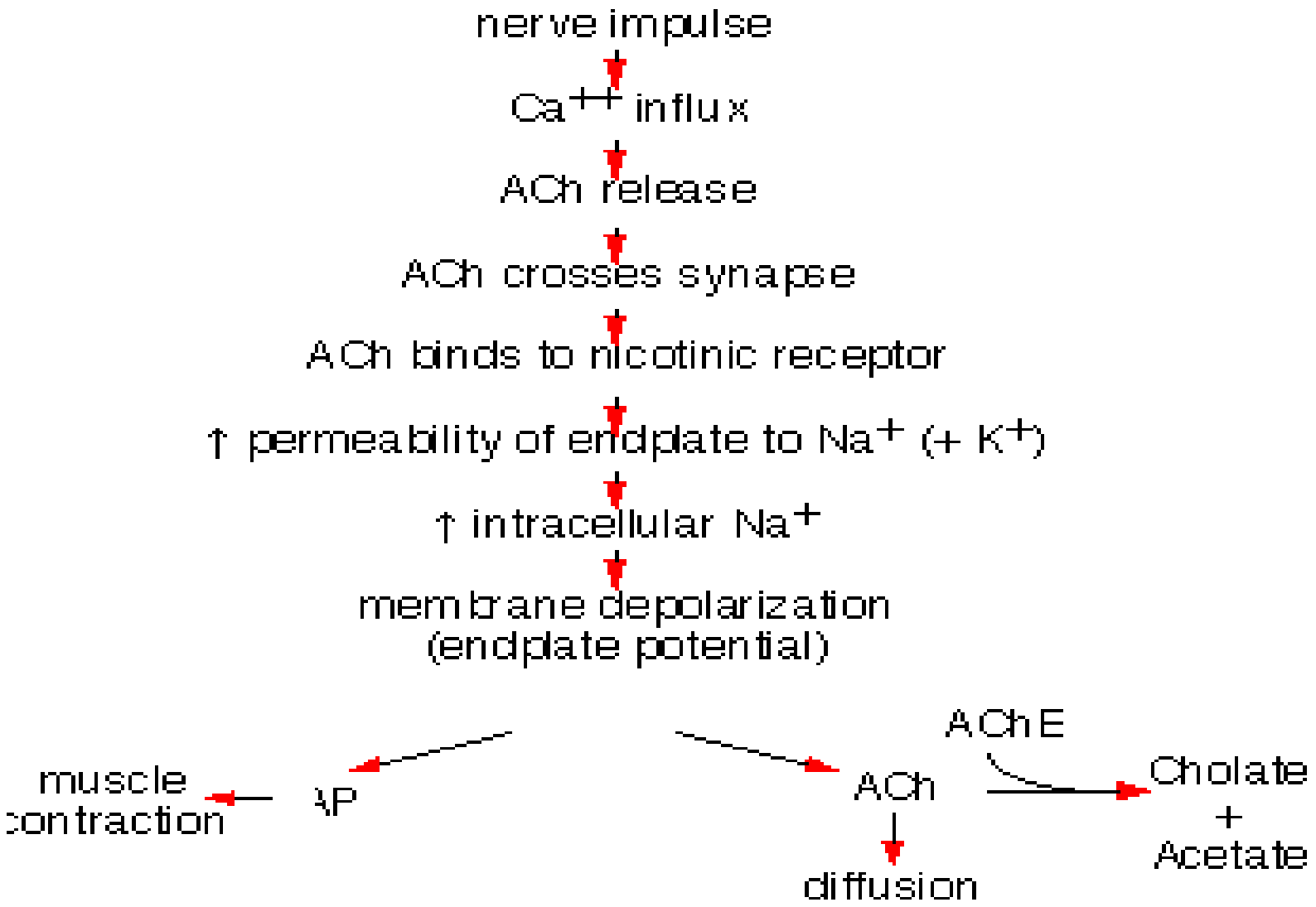
Neuromuscular Blockers

- -These are used during surgery to decrease the amount of anesthetic agent required, increase safety and increase recovery

Neuromuscular Junction



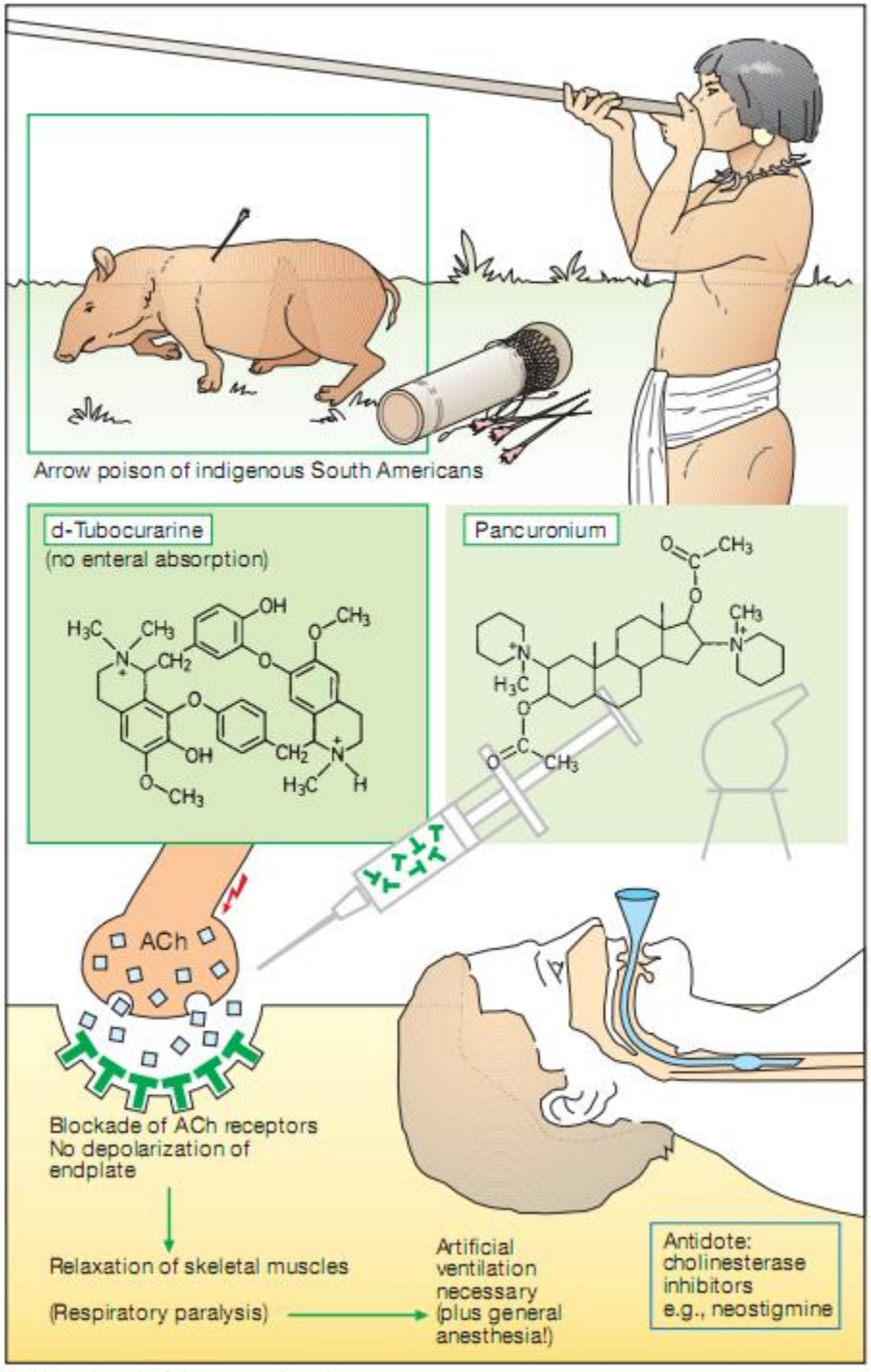

N2-Ligand-gated ion channel: at Neuromuscular Junction.
Na+
ACh
ACh
δ
γ
α
α
β
5-subunits
4-TMDs each
Outside
Inside
Ach opens Na+ channel causing depolarization and subsequent action potential at NMJ.
N2-nicotinic NMJ binds to: decamethonium > hexamethonium
Na+


nerve impulse
Ca++ influx
ACh release
ACh crosses synapse
ACh binds to nicotinic receptor
↑ permeability of endplate to Na+ (+ K+)
↑ intracellular Na+
membrane depolarization
(endplate potential)
muscle
contraction
AP
ACh
AChE
Cholate
+
Acetate
diffusion

1. Nondepolarizing (competitive) blocking agents (antagonists-curare like)

- -block ACh binding to nicotinic cholinergic receptor on muscle cells
- -dosage of drug depends on agent, muscle location and patient
- -reversal of blockade by concentration of ACh at end-plate membrane by **anticholinesterases** eg. neostigmine, edrophonium

Curare is plant extract from *Chondrodendron tomentosum, Strychnos toxifera etc.* It is used by South America tribals as arrow poison for game hunting. The animals got paralyzed even if not killed by the arrow. Muscle paralyzing active principles of curare are **alkaloids tubocurarine, toxiferine** etc.



2. Depolarizing blocking agents

- -**succinylcholine** is prototype agent
  -effects similar to ACh but longer effect
  -nicotinic agonist (not antagonist) ----> flaccid paralysis

Mechanism:

- **Phase I Block**

binding of succinylcholine to nicotinic receptors

↓

opening of ion channels & Na+ influx

↓

depolarization of muscle cell end-plate membrane

↓

generalized disorganized contraction of motor muscles

↓

not metabolized by AChE, slow enzyme hydrolysis by pseudocholinesterase

↓

membranes remain depolarized & unresponsive

↓

flaccid paralysis

Mechanism:

- **Phase II Block**

repeated dosing &increased concentration of succinylcholine

↓

Decreased endplate depolarization

↓

repolarization of membrane

↓

membrane becomes desensitized
.: depolarization by ACh cannot occur

- -**Succinylcholine** is metabolized by plasma **pseudocholinesterase**
  -activity of pseudocholinesterase may be abnormal due to genetic abnormalities, trauma, alcoholism, pregnancy
- **.:** blockade may be lengthened or shortened

Effects of neuromuscular blocking drugs

Skeletal muscles. Intravenous injection of competitive blockers rapidly produces muscle weakness, followed by flaccid paralysis.

The action of SCh develops very rapidly. Apnoea occurs within 45–90 sec, but lasts only 2–5 min and recovery is rapid.

Order of paralysis of muscles:

1. Eye, face
2. Fingers, limbs, neck,
3. Trunk muscles
4. Intercostal muscles and diaphragm

- -recovery in reverse order
  -degree of blockade may be influenced by patient age, renal function, presence of anesthetic agents etc

Autonomic ganglia. Competitive blockers can produce some degree of ganglionic blockade. SCh as an agonist of N-receptors may cause ganglionic stimulation.

Histamine release with hypotension and bronchospasm can cause tubocurarine from the mast cells. This does not involve the immune system.

CVS. Tubocurarine produces significant fall in BP and sometimes – tachycardia (due to vagal ganglionic blockade). SCh initially produces bradycardia due to activation of vagal ganglia, followed by tachycardia and rise in BP, due to stimulation of sympathetic ganglia.

GIT. The ganglion blocking action of competitive agents may enhance postoperative paralytic ileus after abdominal operations.

Pharmacokinetics

All neuromuscular blockers are quaternary compounds. They are not absorbed in GIT, do not cross placental, and BBB. The unchanged drug is excreted in urine, and bile.

SCh is rapidly hydrolyzed by plasma pseudocholin-esterase to succinylmonocholine and then to succinic acid and choline (the action lasts 3–5 min). Some patients (1:3000) have genetically determined abnormality (low affinity for SCh) or deficiency of pseudocholin-esterase. In these patients SCh causes dominant phase II blockade, resulting in muscle paralysis and apnoea, lasting hours. In this case the intubation of the patient must be continuous until full recovery.

Indications

- The most important use of neuromuscular blockers is as *adjuvant drugs to general anaesthesia*. Surgical procedures are performed more safely and rapidly.

Surgical uses:

1. endotracheal intubation
2. maintenance of controlled ventilation during surgery
3. Decreased muscle contraction at surgical site
4. long-term controlled ventilation in intensive care units

- *The competitive neuromuscular blockers* are particularly helpful in abdominal and thoracic surgery, intubation and endoscopies, orthopedic procedures.

- *SCh* is employed for brief procedures, e.g. endotracheal intubation, laryngoscopy, bronchoscopy, esophagoscopy, reduction of fractures, and dislocations.

- *SCh* is mostly used to avoid convulsions and trauma from electroconvulsive therapy.

- In severe cases of tetanus and status epilepticus, which are not controlled by diazepam or other anticonvulsive drugs, *competitive neuromuscular blockers are used*.

Main drug interactions

- There is *in vitro* incompatibility between SCh and thiopental (thiopentone).
- General anaestetics, aminoglysides (gentamicin, tobramycin, etc.) and hypokalemic diuretics potentiate competitive blockers.
- ***Anti-ChEs (galantamine, neostigmine) and amino-pyridine (Pymadine®) reverse the action of competitive neuromuscular blockers.***
- ***SCh potentiates malignant hyperthermia, produced by halothane.***
- Calcium channel blockers potentiate both depolarizing and nondepolarizing neuromuscular blockers.

Adverse effects

- Hyperthermia: (halotan+succinylcholine)

Treatment of malignant hyperthermia- rapidly cooling the patient, administration of dantrolen which blocks release of calcium from the sarcoplasmic reticulum of muscle cells, thereby reducing heat production and relaxing muscle tone

- Apnea

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

- Hyperkalemia:

Succ. İncreases potassium release from intracellular stores