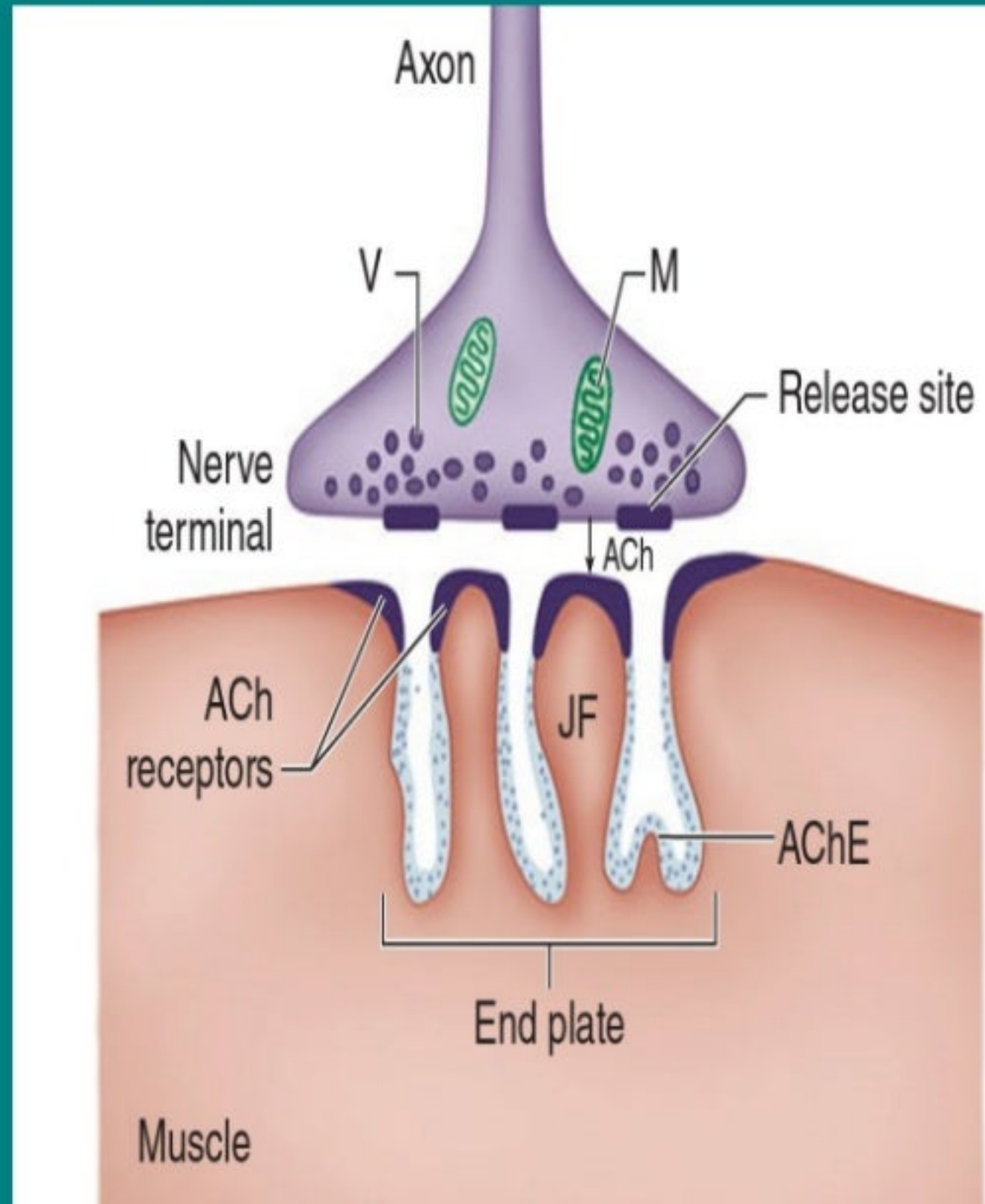


# NEUROMUSCULAR BLOCKING AGENTS

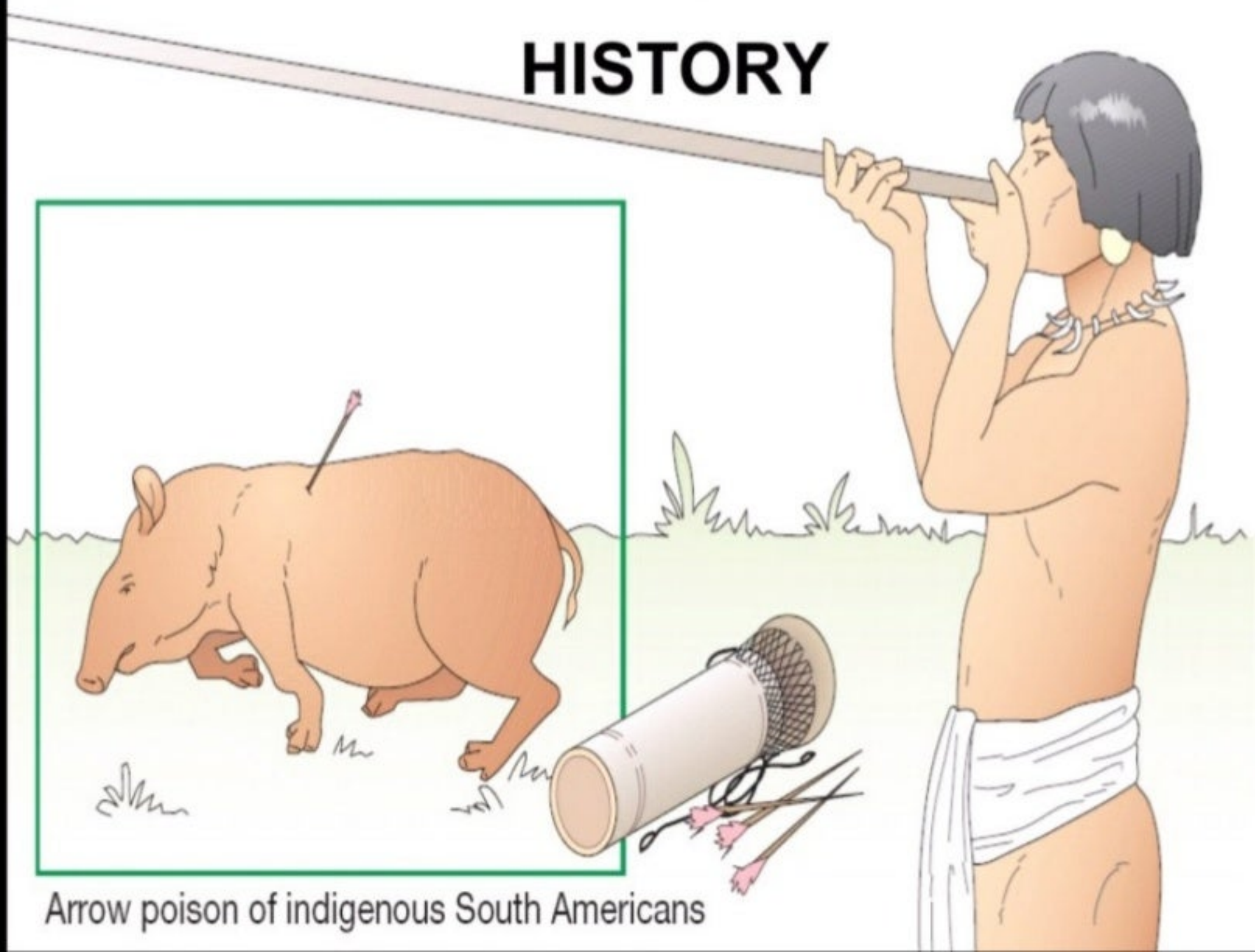


PRESENTED BY:

DR.JAGADISH JENA

DEPT.OF ANAEST.& CR.CARE  
VIMSAR,BURLA

# HISTORY



Arrow poison of indigenous South Americans



# HISTORY

- In 1942 **Griffith & Johnson** suggested that d-tubocurarine is a safe drug to use during surgery.
- Succinylcholine for the first time introduced by **Thesleff & by Foldes** & colleagues in 1952.
- In 1962 **Baird & Reid** first administered pancuronium
- Vecuronium, an amino steroid & atracurium, a benzylisoquinolinium introduced in **1980** and
- Mivacurium introduced in **1990**.
- All modern agents are entirely synthetic

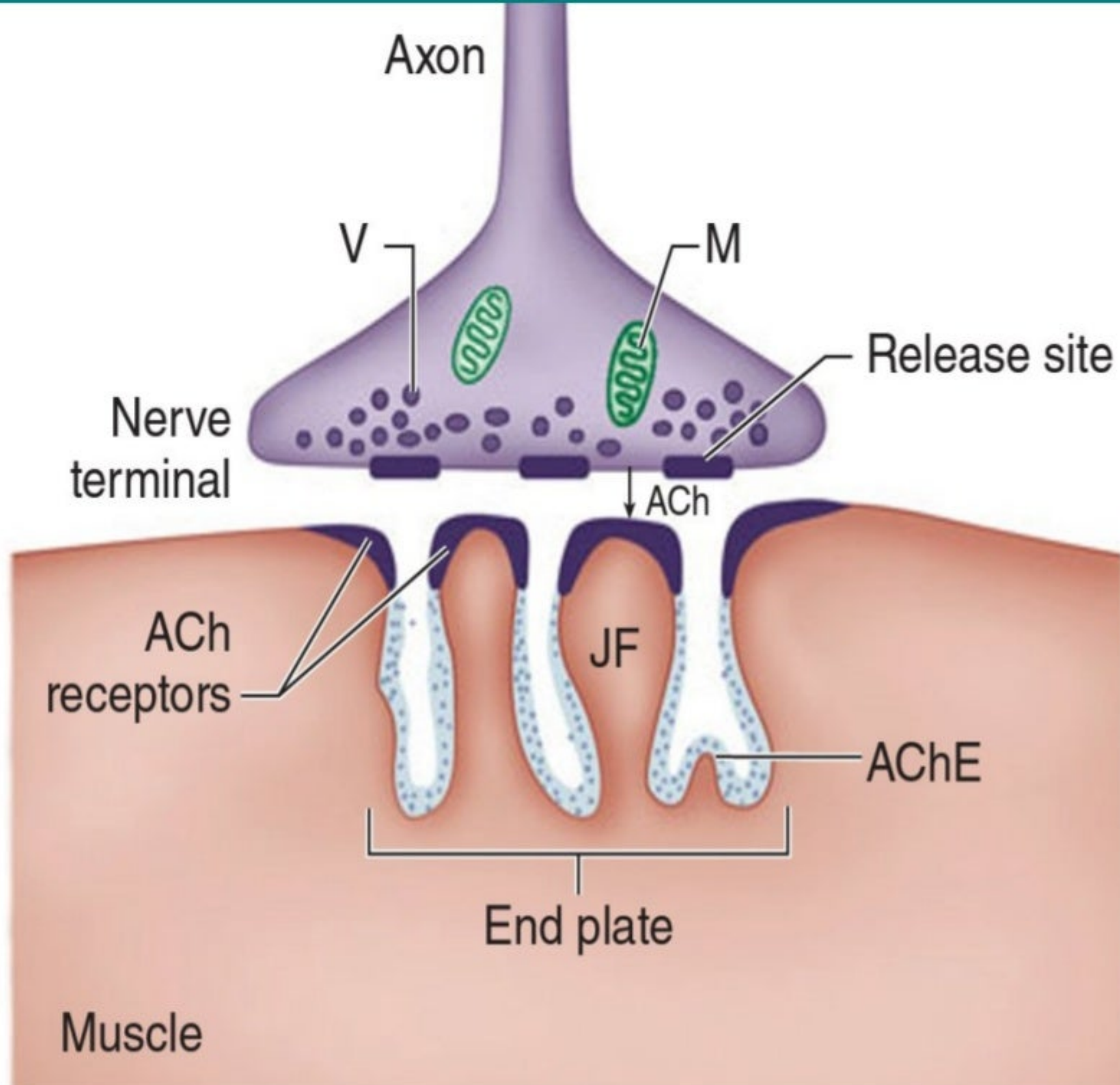


Definition: NMBA are the drugs that act peripherally at **NM-Junction** and muscle fiber itself to block neuromuscular transmission.

**Why do we need them ?**

In order to facilitate muscle relaxation for surgery and mechanical ventilation during surgery & in ICU.





# Neuromuscular junction

- Association between a motor neuron and a muscle cell.
- **Synaptic cleft.:** The cell membranes of the neuron and muscle fiber are separated by a narrow (20-nm) gap.
- The neurotransmitter responsible for neurotransmission at the neuromuscular junction is acetylcholine.
- It is synthesized in the cytoplasm by combination of choline and coenzyme A with the help of choline acetyl transferase.
- These synthesized acetylcholine stored in vesicles.
- A single vesicle contains about a quantum of Ach .



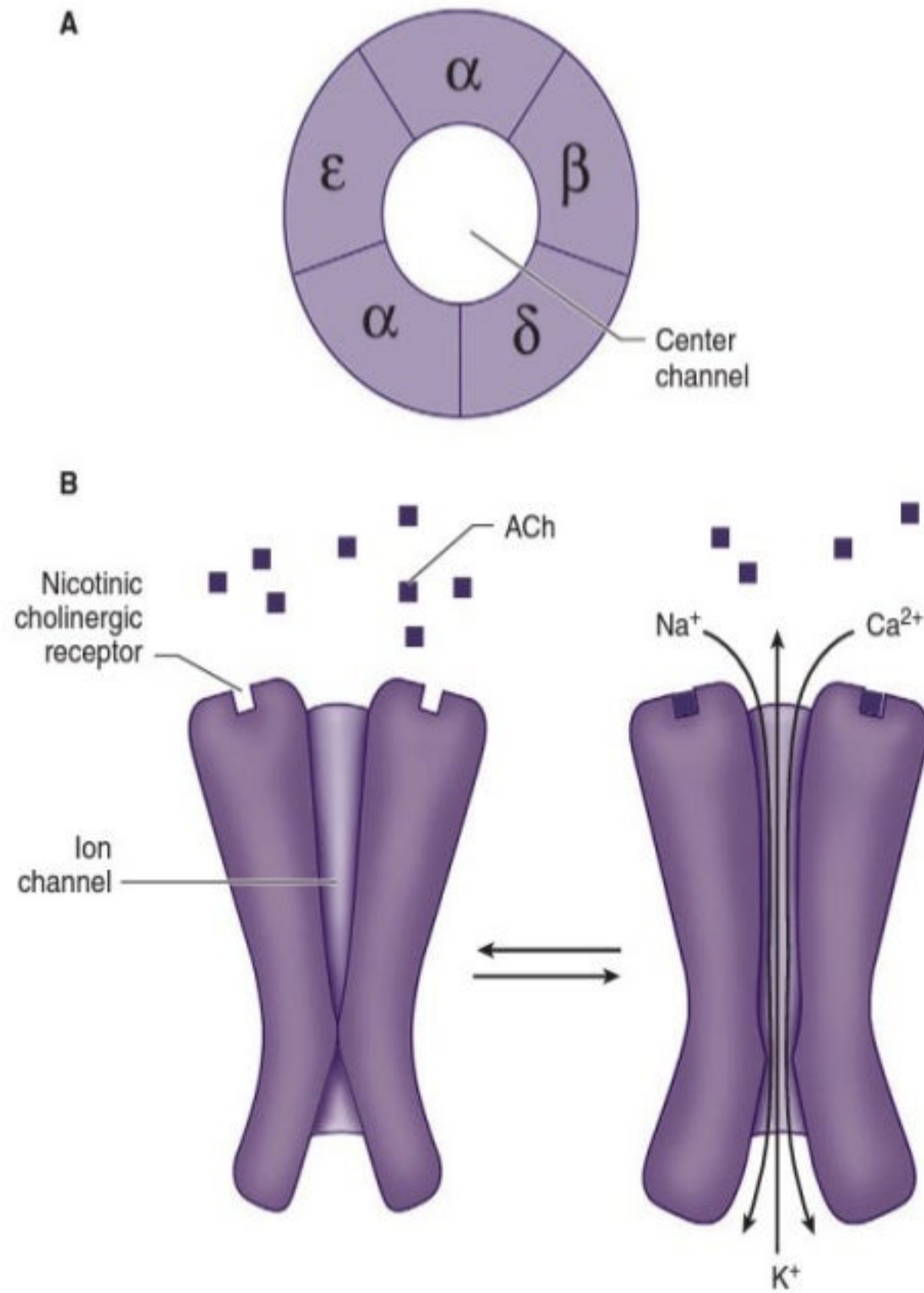
- As a nerve's action potential depolarizes its terminal, an influx of calcium ions through voltage-gated calcium channels into the nerve cytoplasm allows storage vesicles to fuse with the terminal plasma membrane and release their contents.
- The ACh molecules diffuse across the synaptic cleft to bind with nicotinic cholinergic receptors on a specialized portion of the muscle membrane at the motor end-plate.
- Each neuromuscular junction contains approximately 5 million of these receptors.
- Among these minimum 500000 receptors required to be activated for normal muscle contraction.



# Structure of ACh receptors

- Each ACh receptor in the neuromuscular junction normally consists of five protein subunits; two  $\alpha$  subunits; and single  $\beta$ ,  $\delta$ , and  $\epsilon$  subunits.
- Only the two identical  $\alpha$  subunits are capable of binding ACh molecules.
- If both binding sites are occupied by ACh, a conformational change in the subunits, briefly (1 ms) opens an ion channel in the core of the receptor.
- The channel will not open if ACh binds on only one site.



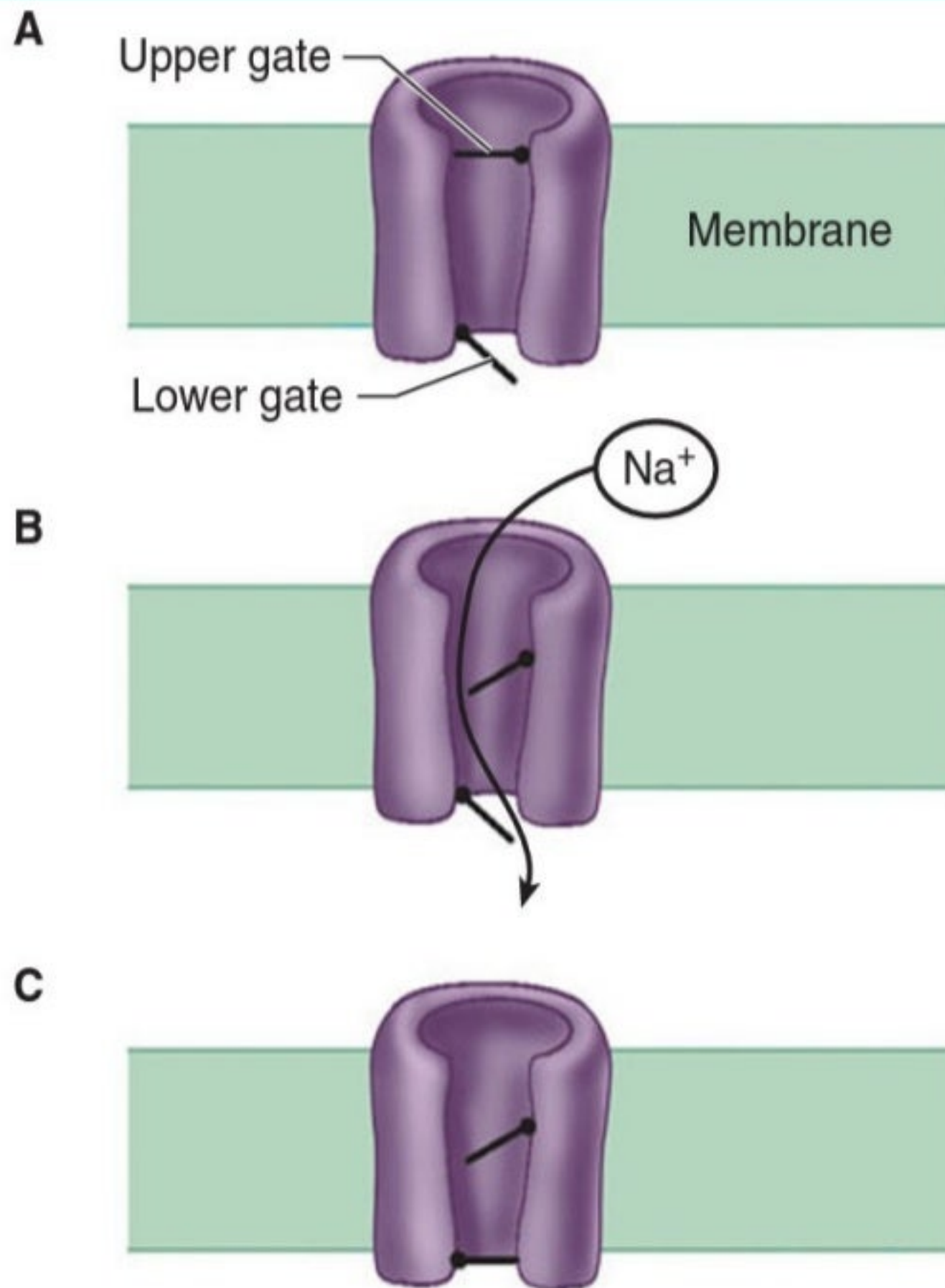


**FIGURE 11-2** **A:** Structure of the ACh receptor. Note the two  $\alpha$  subunits that actually bind ACh and the center channel. **B:** Binding of ACh to receptors on muscle end-plate causes channel opening and ion flux.

- Another isoform of ACh contains a  $\gamma$  subunit instead of the  $\epsilon$  subunit known as fetal or immature receptor, because this form initially expressed in fetal muscle.
  - It is also often referred to as extrajunctional receptors.
- Cations flow through the open ACh receptor channel (sodium and calcium in; potassium out), generating an **end-plate potential**.
- When enough receptors are occupied by ACh, the end-plate potential will be sufficiently strong to depolarize the perijunctional membrane.



- Sodium channels are present in muscle membrane.
- Perijunctional areas of muscle membrane have a higher density of these sodium channels than other parts of the membrane.
- These sodium channels have two types of gate
  - voltage dependent
  - time dependent
- Sodium ions pass only when both gates are open.



- **sodium channel** is a transmembrane protein that can be conceptualized as having **two gates**.
- Sodium ions pass only when both gates are open.
- Opening of the gates is time dependent and voltage dependent.
- The channel therefore possesses **three functional states**.
- A...**At rest**, the lower gate is open but the upper gate is closed
- B...reaches threshold voltage **depolarization**, the upper gate opens and sodium can pass
- C...Shortly after the upper gate opens the **timedependent lower gate closes**



- With the opening of sodium channels and entry of sodium, calcium ions release from sarcoplasmic reticulum.
- This intracellular calcium allows the contractile proteins actin and myosin to interact, bringing about muscle contraction.

# Steps in normal NM transmission.

Nerve action potential is transmitted, and the **nerve terminal is depolarized.**

**Ach is released** from storage vesicles at the nerve terminal. Enough ach is released to bind 500,000 receptors.


Ach molecules bind to the  $\alpha$  subunits of the ach receptor on the **post junctional membrane, generating a conformational change** and

**Opening receptor channels.** Receptors do not open unless both  $\alpha$  receptors are occupied by ach

Sodium and calcium flow through the open receptor channel generating an **end-plate potential.**



When between **5% and 20%** of the receptor channels are open and a threshold potential is reached, .... **Voltage-gated sodium channels** within perijunctional portion of the muscle membrane open



when a threshold voltage is developed across them, a **muscle action potential (MAP) is generated**



**ACh is rapidly hydrolyzed** into acetate and choline by the substrate-specific enzyme **acetylcholinesterase**.



After unbinding ACh, the **receptors' ion channels close**, permitting the **end-plate to repolarize**. Calcium is resequestered in the sarcoplasmic reticulum, and the **muscle cell relaxes**.

# Classification-mechanism & duration of action

## Depolarizing

### *Short-acting*

- Succinylcholine

## Nondepolarizing

### *Short-acting*

- Gantacurium
- Mivacurium

### *Intermediate-acting*

- Atracurium
- Cisatracurium
- Vecuronium
- Rocuronium

### *Long-acting*

- Pancuronium
- Pipecuronium
- Doxacurium



# MECHANISM OF ACTION of depolarizing NMBA

1

- Depolarizing muscle relaxants closely resemble ACh and readily bind to ACh receptors, generating a muscle action potential.

2

- Unlike ACh, however, these drugs are not metabolized by acetylcholinesterase, and their concentration in the synaptic cleft does not fall as rapidly, resulting in a prolonged depolarization of the muscle end-plate.

3

- Continuous end-plate depolarization causes muscle relaxation

4

- because opening of perijunctional sodium channels is time limited (sodium channels rapidly “inactivate” with continuing depolarization)



# Phases of block in Depolarizing NMBA

## Phase-1 block

- Perijunctional sodium channel cannot reopen until the end-plate repolarizes.
- The end-plate cannot repolarize as long as the depolarizing muscle relaxant continues to bind to ACh receptors; this is called a phase I block.

## Phase ii Block

- After a period of time, prolonged end-plate depolarization can cause poorly understood changes in the ACh receptor that result in a phase II block,



# Mechanism of action of non-depolarizing NMBA

depolarizing muscle relaxants act as ACh receptor agonists, whereas nondepolarizing muscle relaxants function as **competitive antagonists**.



Nondepolarizing muscle relaxants bind ACh receptors but are **incapable of inducing the conformational change necessary for ion channel opening**.



Neuromuscular **blockade occurs even if only one  $\alpha$  subunit is blocked**.



Because ACh is prevented from binding to its receptors, **no end-plate potential develops**.

# OTHER MECHANISMS OF NEUROMUSCULAR BLOCKADE

Interference with the **function of the Ach receptor without acting as an agonist or antagonist.**

Interfere with normal functioning of the **Ach receptor binding site or with the opening and closing of the receptor channel.**

- Example....
  - Inhaled anesthetic agents
  - local anesthetics
  - ketamine.



## closed or open channel blockade

- ***During closed channel blockade***
  - the drug physically plugs up the channel, preventing passage of cations
  - whether or not ACh has activated the receptor.
- ***Open channel blockade***
  - use dependent,
  - because the drug enters and obstructs the ACh receptor channel only after it is opened by ACh binding
- **Example**...channel block in the laboratory include
  - neostigmine,
  - some antibiotics,
  - cocaine, and
  - quinidine.

Other drugs may impair the presynaptic release of ACh

## TABLE 20-2 CHARACTERISTICS OF PHASE I DEPOLARIZING BLOCKADE

Decreased twitch amplitude

Absence of fade with continuous (tetanic) stimulation

Similar decreases in the amplitude of all twitches in the train-of-four ratio ( $>0.7$ )

Absence of posttetanic potentiation

Antagonism by nondepolarizing muscle relaxants

Augmentation by anticholinesterase drugs



## TABLE 20-3 CHARACTERISTICS OF THE NONDEPOLARIZING NEUROMUSCULAR BLOCKADE

- Decreased twitch amplitude
- Fade with continuous (tetanic) stimulation
- Train-of-four ratio  $<0.7$
- Posttetanic potentiation
- Absence of fasciculations
- Antagonism by anticholinesterase drugs
- Augmentation by other nondepolarizing muscle relaxants

# SEQUENCE OF MUSCLE BLOCKADE

- First muscle to be blocked by both depolarising and non depolarizing muscle relaxants are the central muscles then peripheral muscles blocked.
- So the sequence of blockade is...  
**FACE – JAW – PHARYNX-LARYNX –  
RESPIRATORY – TRUNK MUSCLES – LIMB  
MUSCLES**
- At recovery these recover in the same order.



# Depolarizing NMBA

(Suxamethonium)

# SUCCINYLCHOLINE

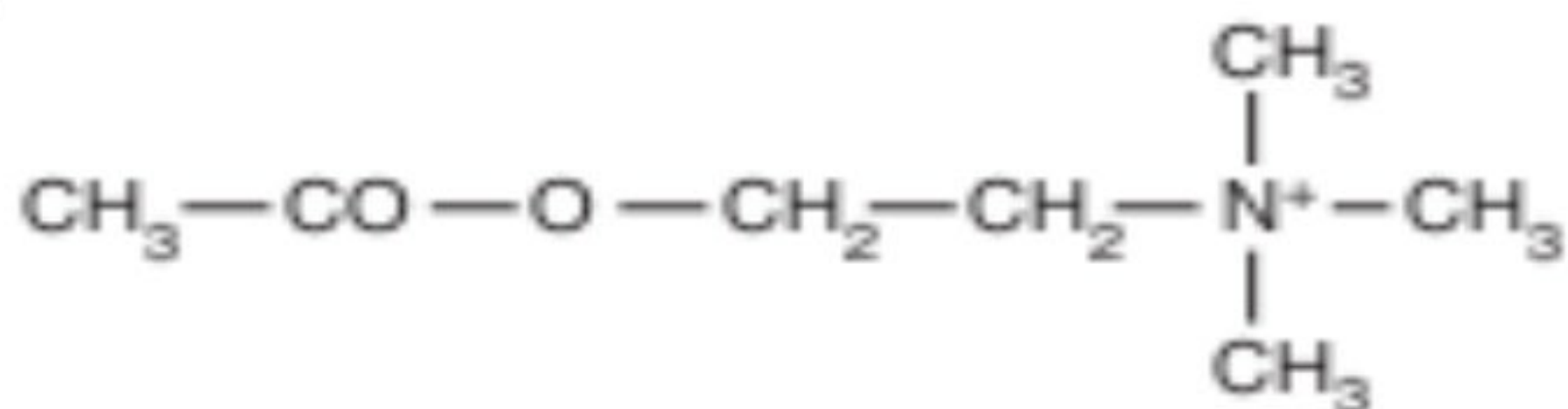
Succinylcholine is a quaternary ammonium compound—also called diacetylcholine or suxamethonium—

- consists of two joined ACh molecules

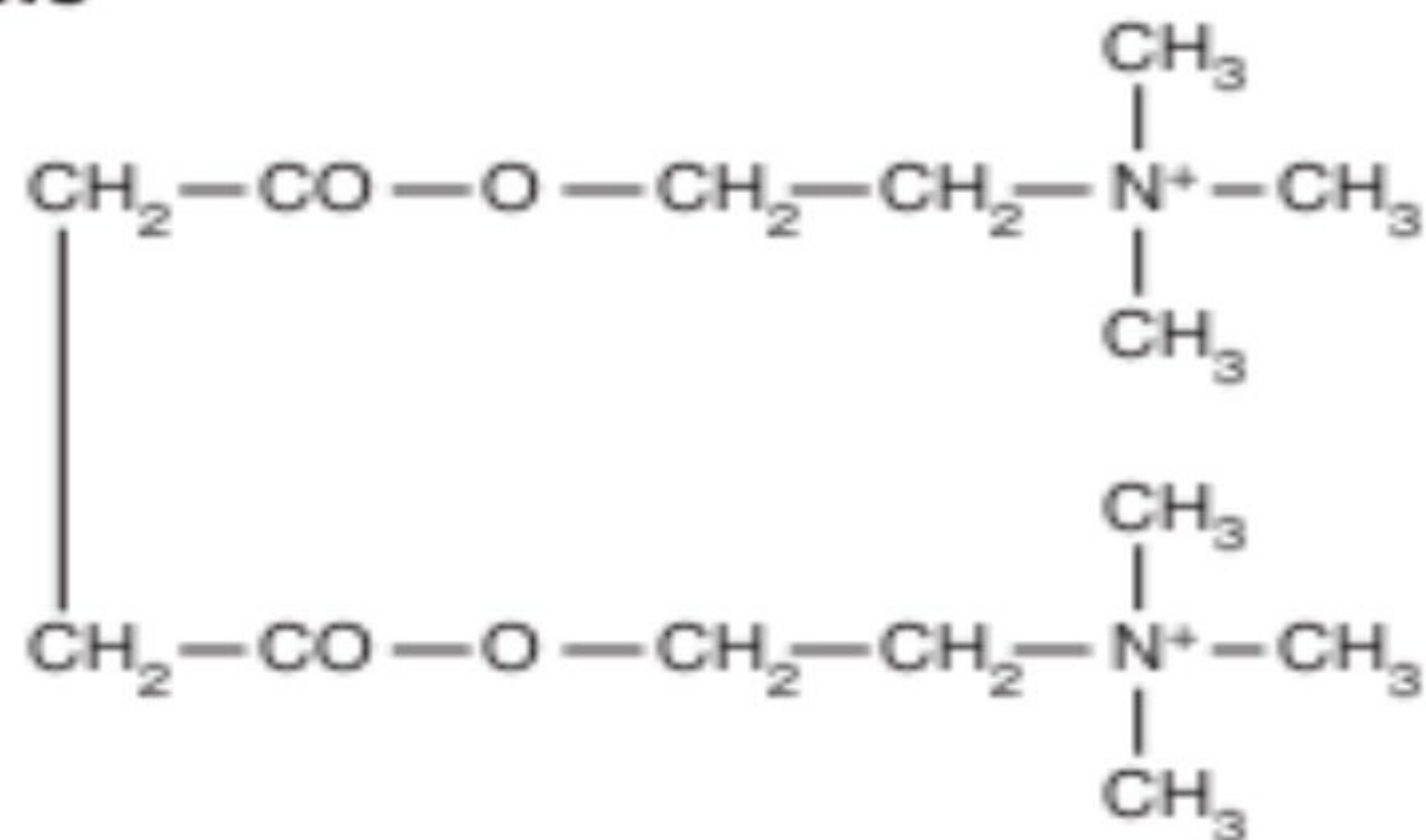
only depolarizing relaxant now available in clinical practice is succinylcholine.



## Acetylcholine



## Succinylcholine



# Mechanism of action

Depolarizing muscle relaxants very closely resemble ACh and readily bind to ACh receptors, generating a muscle action potential



**Phase i block**



**Phase ii block**



# Metabolism & Excretion

Rapid onset of action (30–60 s) and

- Small volume of distribution due to its very low lipid solubility
- Relative overdose that is usually administered.

Short duration of action (usually less than 10 min).

In circulation.....Rapidly metabolized by pseudocholinesterase into succinylmonocholine.

- As the drug level fall in blood, succinylcholine molecules diffuse away from the neuromuscular junction, limiting the duration of action.

- However duration of action can be prolonged or prolonged apnea after succinylcholine can occur due to the following conditions:
  - low pseudocholinesterase
  - atypical pseudocholinesterase
  - high dose or phase 2 block
  - hypothermia



# Decreased level of pseudocholinesterase

Reduced pseudocholinesterase levels...Generally produce only modest prolongation of succinylcholine's actions (2–20 min).

- Pregnancy,
- Liver disease,
- Renal failure,
- Malignancies
- Hypoproteinemia
- Hypothyroidism.,
- Alcoholics

## Certain drug therapies

- Echothiophate.....Organophosphate use for glaucoma
- Neostigmine ,pyridostigmine....Cholinesterase inhibitors
- Phenelzine.....Monoamine oxidase inhibitor
- Cyclophosphamide....Anti neoplastic
- Metoclopramide...Antiemetic & prokinetic
- Esmolol...Beta blocker
- Pancuronium....Non depolarizing nmba
- Oral contraceptives



# Atypical/Abnormal pseudocholinesterase

Structure of plasma cholinesterase is determined genetically, by **autosomal genes**,

## **1.Heterozygote** for the atypical gene

- One in 25-30 patients of european extraction is a heterozygote with one normal and one abnormal (atypical) pseudocholinesterase gene, resulting in a slightly prolonged block (20–30 min)

**2.Homozygous atypical pseudocholinesterase gene**.....1 in 3000 patients have two copies of the abnormal gene (homozygous atypical) that produce an enzyme with little or no affinity for succinylcholine.

- Will have a very long blockade eg, 4–8 h



# Measurement of Atypical Pseudocholinesterse

1. Quantitative....determined in the laboratory quantitatively in units per ml (a minor factor)

2. Qualitative.....qualitatively by **dibucaine number** (the major factor)



# Dibucaine Number

**Percentage of inhibition** of pseudocholinesterase activity by Dibucaine is termed as dibucaine number

Dibucaine, a local anesthetic, **inhibits normal pseudocholinesterase activity by 80%**, but inhibits atypical enzyme activity by only 20%.

Serum from an individual who is **heterozygous for the atypical enzyme** is characterized by an intermediate **40% to 60% inhibition**



# Management of succinylcholine Apnoea

This condition is not life-threatening, but the **risk of awareness** is considerable

- especially after the end of surgery, when the anaesthesiologist, who may not yet have made the diagnosis, is attempting to waken the patient.

**Anaesthesia must be continued** until full recovery from neuromuscular block is demonstrable.

- In such patients, non-specific esterases (10% metabolism) gradually clear the drug from plasma.


source of cholinesterase, such as **fresh frozen plasma**, should be administered



plasma sample should be taken..... Quantitative & Qualitative measurements of Atypical cholinesterase



Prolonged paralysis from succinylcholine caused by abnormal pseudocholinesterase (atypical cholinesterase) should be treated with **continued mechanical ventilation and sedation** until muscle function returns to normal by clinical signs.



**monitor neuromuscular transmission accurately**, until full recovery from residual neuromuscular block.



patient who is found to have reduced enzyme activity and structurally abnormal enzyme, should be given a **warning card or alarm bracelet**



# Drug interaction special considerations

**1. Cholinesterase Inhibitors.....**markedly prolong a depolarizing phase I block by two mechanisms.

- 1. inhibiting acetylcholinesterase....higher ACh concentration at the nerve terminal, which intensifies depolarization
- 2. inhibiting pseudocholinesterase....reduce the hydrolysis of succinylcholine

## Example

- Organophosphate pesticides, for .....irreversible inhibition of acetylcholinesterase and can prolong the action of succinylcholine by 20–30 min.
- Echothiophate eye drops.....can markedly prolong succinylcholine



## 2. Nondepolarizing Relaxants

small doses of nondepolarizing relaxants

- antagonize a depolarizing phase I block. ....drugs occupy some ACh receptors,.....so
- partial prevention of depolarization by succinylcholine

If enough depolarizing agent is administered..... to develop a phase II block,

- then a nondepolarizer will potentiate paralysis.



# Drug Interactions

**TABLE 11-4 Potentiation (+) and resistance (–) of neuromuscular blocking agents by other drugs.**

Drug	Effect on Depolarizing Blockade	Effect on Nondepolarizing Blockade	Comments
Antibiotics	+	+	Streptomycin, aminoglycosides, kanamycin, neomycin, colistin, polymyxin, tetracycline, lincomycin, clindamycin
Anticonvulsants	?	–	Phenytoin, carbamazepine, primidone, sodium valproate
Antiarrhythmics	+	+	Quinidine, calcium channel blockers
Cholinesterase inhibitors	+	–	Neostigmine, pyridostigmine
Dantrolene	?	+	Used in treatment of malignant hyperthermia (has quaternary ammonium group)
Inhalational anesthetics	+	+	Volatile anesthetics
Ketamine	?	+	
Local anesthetics	+	+	High doses only
Lithium carbonate	+	?	Prolongs onset and duration of succinylcholine
Magnesium sulfate	+	+	Doses used to treat preeclampsia and eclampsia of pregnancy

# Dosage & Storage

usual **adult dose of** succinylcholine for **intubation** is 1-2 mg/kg intravenously.

- Doses as small as 0.5 mg/kg will often provide acceptable intubating conditions if a defasciculating dose of a nondepolarizing agent is not used.

**Repeated small boluses (10 mg) or a succinylcholine drip** (1 g in 500 or 1000 mL, titrated to effect) can be used during surgical procedures that require brief but intense paralysis

- Such as ENT procedures...endoscopy
- Neuromuscular function should be frequently monitored with a nerve stimulator to prevent overdosing and to watch for phase II block.



**Pediatric patients** are often need greater dose than for adults because they have a larger extracellular space than adults

**Intramuscularly** to children a dose as high as 4–5 mg/kg does not always produce complete paralysis

## Storage...

- Stored under refrigeration (2–8°C), and should be used within 14 days after removal from refrigeration and exposure to room temperature.

# Side Effects & Clinical Considerations

Succinylcholine is still useful for **rapid sequence induction** and for **short periods of intense paralysis**

succinylcholine is considered relatively contraindicated in the routine management of **children and adolescent** patients having undiagnosed myopathies



# 1. Cardiovascular

Suxamethonium acts on **cholinergic ach receptors** in addition to those at the neuromuscular junction

- Entire parasympathetic nervous system and
- Parts of the sympathetic nervous system
  - Sympathetic ganglions
  - Adrenal medulla
  - Sweat glands



Stimulation of **nicotinic receptors** in parasympathetic and sympathetic ganglia, and **muscarinic receptors** in the sinoatrial node of the heart.....**complex effects**

increase or decrease blood pressure and heart rate.

**Low doses** of succinylcholine can produce negative chronotropic and inotropic effects

**higher doses** usually increase heart rate and contractility and elevate circulating catecholamine levels



**Children** are particularly susceptible to **profound bradycardia** following administration of succinylcholine.

in **adults Bradycardia** will sometimes occur when a **second bolus** of succinylcholine is administered approximately 3–8 min after the first dose

- succinylmonocholine, sensitizes muscarinic cholinergic receptors in the sinoatrial node
- Intravenous atropine (0.02 mg/kg in children, 0.4 mg in adults) is normally given prophylactically to children prior to the first and subsequent doses in adults.

**Arrhythmias**.....nodal bradycardia and ventricular ectopy may occur



# B. Fasciculations

**Onset of paralysis  
by succinylcholine  
signaled by...**

- Visible motor unit contractions called fasciculation

**Prevented by**

- Precurarization

**Not observed in**

- Young children and
- Elderly patients.



# C. Hyperkalemia

## succinylcholine-induced depolarization

- increase serum potassium by 0.5 mEq/L.
- insignificant in patients with normal baseline potassium levels
- can be life-threatening in patients with preexisting hyperkalemia.

## Hyperkalemic cardiac arrest

- can prove to be quite refractory to routine cardiopulmonary resuscitation
- requiring calcium, insulin, glucose and even cardiopulmonary bypass

# Conditions causing susceptibility to succinylcholine-induced hyperkalemia

Burn injury

Massive trauma

Severe intraabdominal infection

Spinal cord injury

Encephalitis

Stroke

Guillain-Barré syndrome

Severe Parkinson's disease

Tetanus

Prolonged total body immobilization

Ruptured cerebral aneurysm

Polyneuropathy

Closed head injury

Hemorrhagic shock with metabolic acidosis

Myopathies (eg, Duchenne's dystrophy)



# Mechanism of hyperkalemia

**Denervation injuries** (spinal cord injuries, larger burns)

**Immature isoform of the Ach receptor** may be expressed inside and outside the neuromuscular junction (up-regulation).

succinylcholine is very sensitive to the immature Ach receptor, results in **extensive potassium release**.

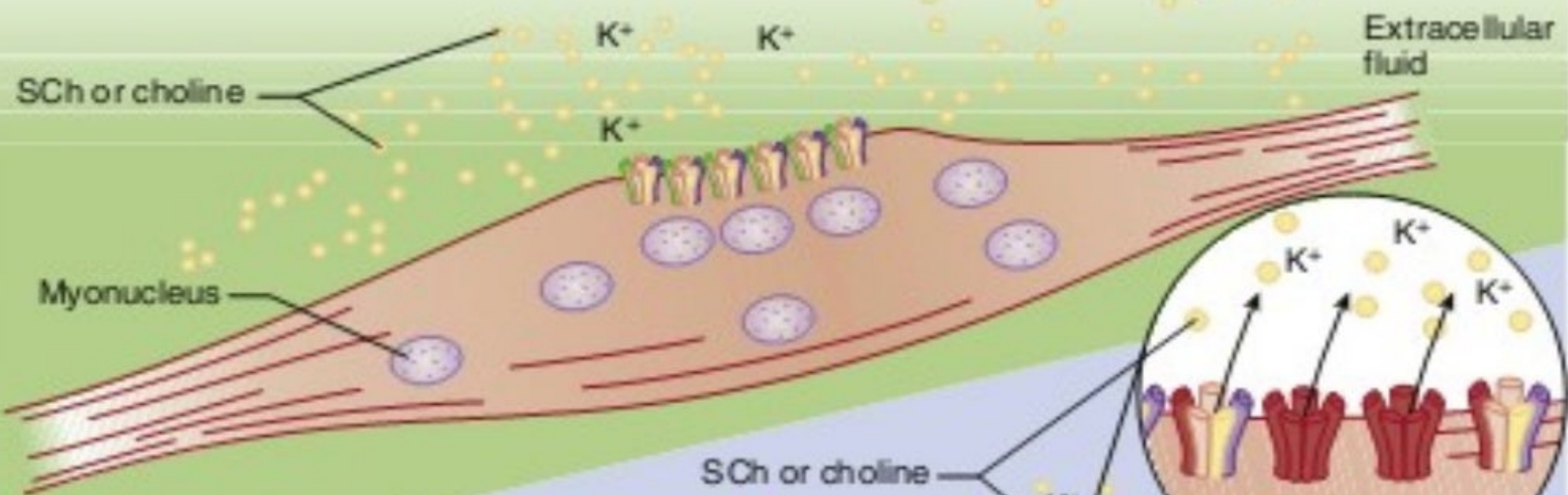
Life-threatening potassium release is **not reliably prevented by pretreatment with a nondepolarizer**

risk of hyperkalemia usually seems to peak in **7–10 days** following the injury

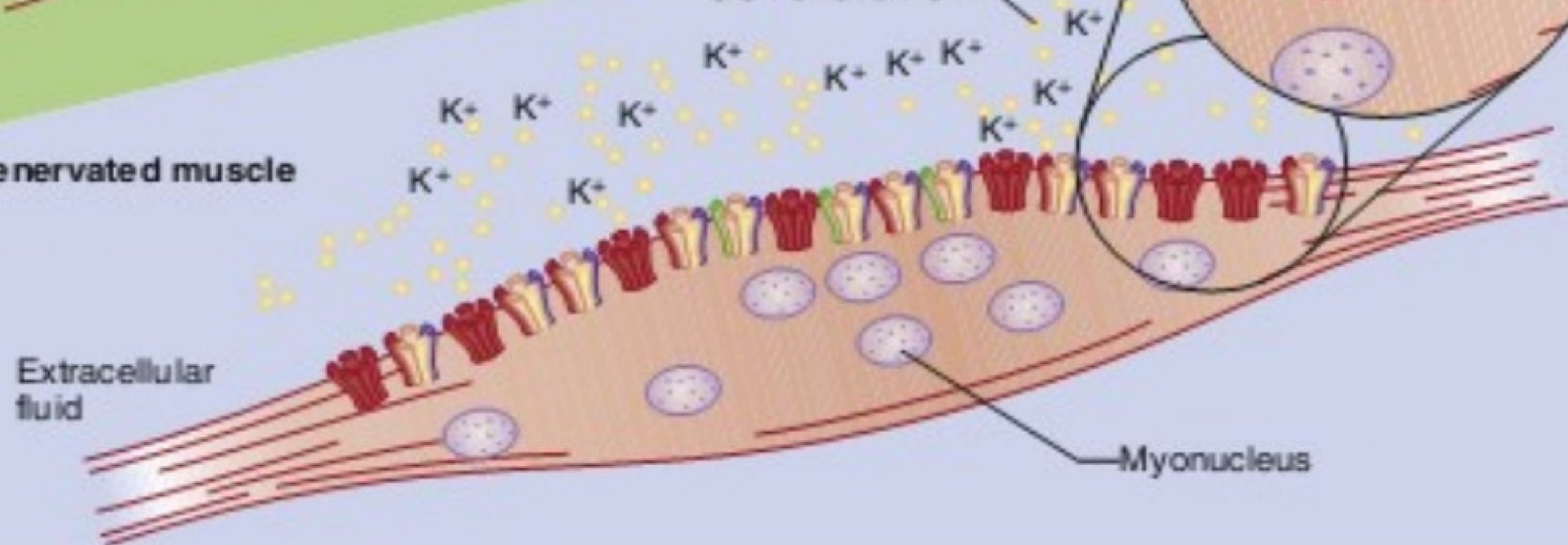
risk of hyperkalemia from succinylcholine is **minimal in the first 2 days** after spinal cord or burn injury.



## Innervated muscle



## Denervated muscle





# D. Muscle Pains

Increased incidence of postoperative myalgia.....Prevention by

- Rocuronium (0.06–0.1 mg/kg) prior to succinylcholine has been reported to be effective

Myalgias are theorized to be due to the initial unsynchronized contraction of muscle groups

- Myoglobinemia and increases in serum creatine kinase can be detected following administration of succinylcholine

Treatment

- Use of nonsteroidal antiinflammatory drugs may reduce the incidence and severity of myalgias.

# E. Intragastric Pressure Elevation

Due to the abdominal wall muscle fasciculations

No evidence that the risk of gastric reflux or pulmonary aspiration is increased by succinylcholine



# F. Intraocular Pressure Elevation

Extraocular muscles have multiple motor end-plates on each cell.

Prolonged membrane depolarization and contraction of extraocular muscles occur

Transiently raise intraocular pressure and theoretically could compromise an injured eye

- No evidence that succinylcholine leads to worsened outcome in patients with “open” eye injuries

## Prevention

- Not always prevented by pretreatment with a nondepolarizing agent.

# G. Masseter Muscle Rigidity

Transiently increases muscle tone in the masseter muscles.

- Some difficulty .... In opening the mouth

Marked increase in tone preventing laryngoscopy is abnormal .....

- Premonitory sign of malignant hyperthermia



# H. Malignant Hyperthermia

Succinylcholine is a potent triggering agent in patients susceptible to malignant hyperthermia.

# I. Intracranial Pressure

Succinylcholine may lead to an **activation of the electroencephalogram**

And Slight **increases in cerebral blood flow and intracranial pressure**



# Prevention

- Increase in intracranial pressure can be attenuated by maintaining good airway control and instituting hyperventilation.
- Pretreating with a nondepolarizing muscle relaxant
- Administering intravenous lidocaine (1.5–2.0 mg/kg) 2–3 min prior to intubation.

Succinylcholine is NOT contraindicated for rapid sequence induction of patients with intracranial mass lesions or other causes of increased intracranial pressure.....

# Nondepolarizing Muscle Relaxants



# Classification- Chemistry

## *Benzylisoquinolinium*

Atracurium

Cisatracurium

Mivacurium

Doxacurium

AV002 (CW002)

Historical interest

- tubocurarine
- metocurine
- gallamine,
- alcuronium, ,
- decamethonium

## *Steroidal*

Pancuronium

Vecuronium

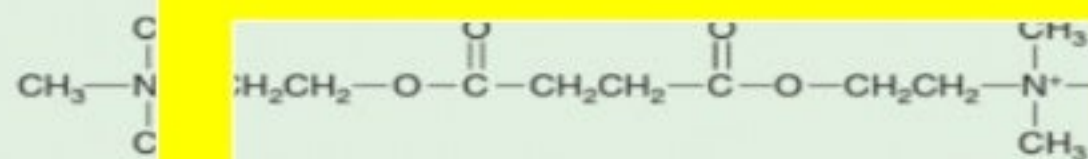
Rocuronium

Pipecuronium

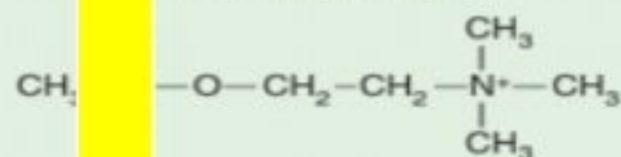
rapacuronium...historical interest

## *Others- chlorofumarates*

Gantacurium



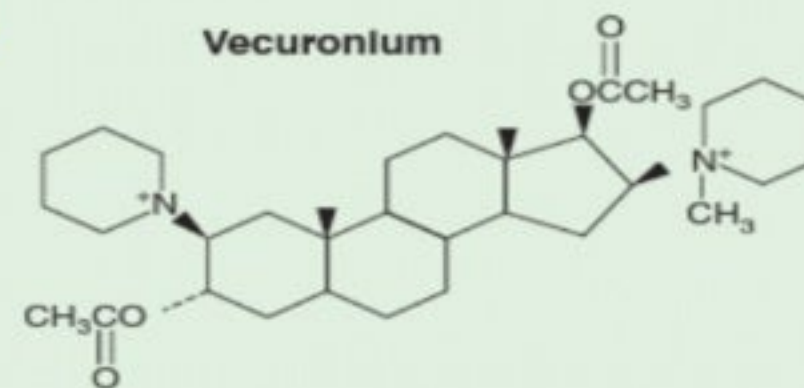
**Acetylcholine**



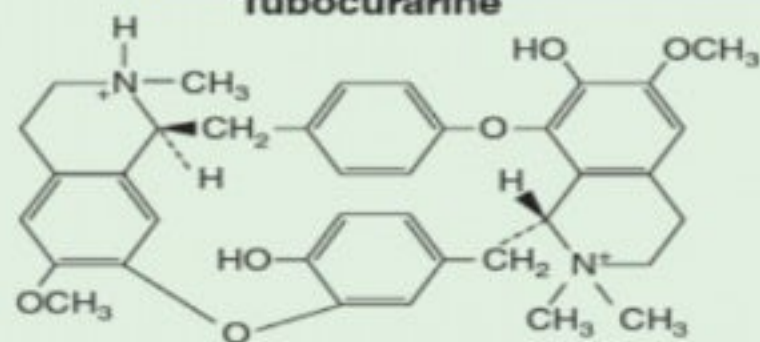
**Pancuronium**



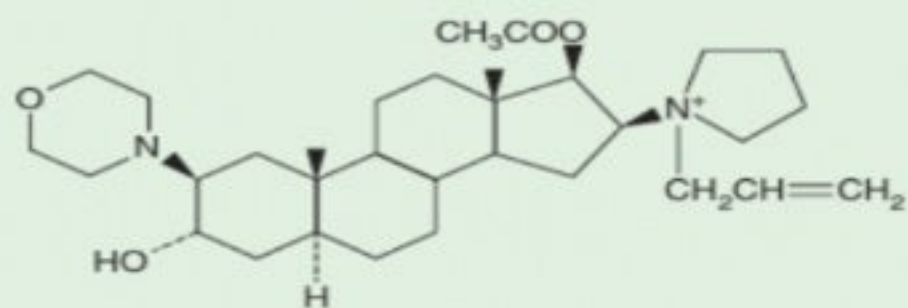
**Vecuronium**



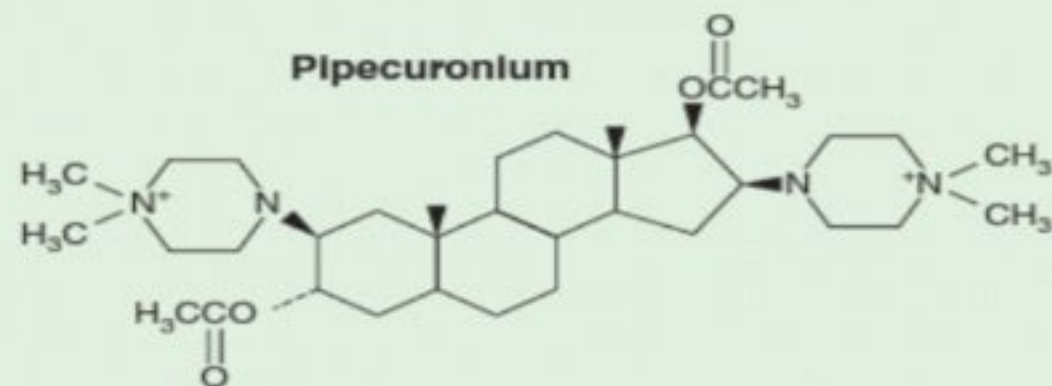
**Tubocurarine**



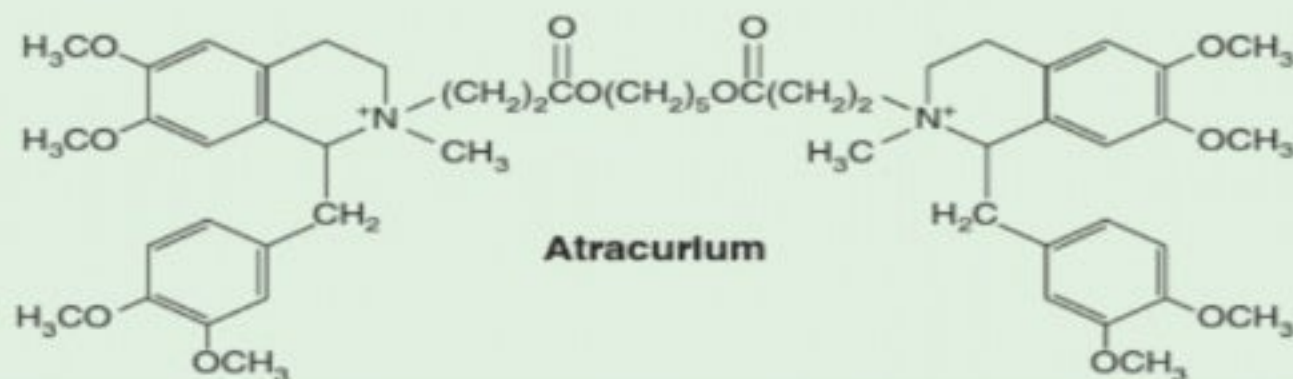
**Rocuronium**



**Pipecuronium**



**Atracurium**





# **Unique Pharmacological Characteristics**

# A. Suitability for Intubation

None of the currently available nondepolarizing muscle relaxants equals succinylcholine

**onset of nondepolarizing relaxants can be quickened** by using

- either a larger dose or
- a priming dose.

Twice the dose of ED95 is usually used for intubation.

**for neuromuscular blockers ED95 is....** the dose that produces 95% twitch depression in 50% of individuals.



# Why potent NMBA has slow onset of action? What is priming dose ?

General rule,..... The **more potent the nondepolarizing muscle relaxant, the slower its speed of onset**

- More the no. Of molecules available at receptors for effect .....More rapid onset
- Less number of molecules will be available at receptors to get the response.....In case of potent drug

**Priming doses...Giving 10% to 15% of the usual intubating dose 5 min before induction will occupy enough receptors so that paralysis will quickly follow when the balance of relaxant is administered.**

- Can produce conditions suitable for intubation as soon as 60 sec following administration of rocuronium or 90 sec following administration of other intermediate-acting nondepolarizers



## B. Suitability for Preventing Fasciculations

To **prevent fasciculations and myalgias**, 10% to 15% of a nondepolarizer intubating dose.....3-5 min before succinylcholine.

**Shortly given before succinylcholine**, prevent myalgias but fasciculations will not be inhibited.

**Rocuronium** has been most popular for precurarization



# C. Maintenance Relaxation

Following intubation, **muscle paralysis may need to be maintained**

- To facilitate surgery, (eg, abdominal operations),
- To permit a reduced depth of anesthesia,
- To control ventilation

## D. Potentiation by Inhalational Anesthetics

Volatile agents decrease nondepolarizer dosage requirements by at least 15%

Actual degree of potentiation depends on...

- **Inhalational anesthetic** (desflurane > sevoflurane > isoflurane and enflurane > halothane > N<sub>2</sub>O / narcotic)
- **Muscle relaxant** employed (pancuronium > vecuronium and atracurium)



# E. Autonomic Side Effects

## Blocking of Autonomic ganglion results in...

- Reducing the ability of the sympathetic nervous system to increase heart contractility and rate in response to hypotension and other intraoperative stresses....Eg, tubocurarine and, to a lesser extent, metocurine

## Block vagal muscarinic receptors in the sinoatrial node....

- Tachycardia. Eg, pancuronium

Newer nondepolarizing relaxants such as atracurium, cisatracurium, vecuronium, and rocuronium, are **devoid of significant autonomic effects**

# F. Histamine Release

Histamine release from mast cells results in...

- bronchospasm
- skin flushing
- hypotension

Pancuronium, atracurium and mivacurium are capable of triggering histamine release, particularly at higher doses

## Prevention

- Slow injection rates
- H<sub>1</sub> and H<sub>2</sub> antihistamine pretreatment



**TABLE 11–6** A summary of the pharmacology of nondepolarizing muscle relaxants.

Relaxant	Chemical Structure <sup>1</sup>	Metabolism	Primary Excretion	Onset <sup>2</sup>	Duration <sup>3</sup>	Histamine Release <sup>4</sup>	Vagal Blockade <sup>5</sup>
Atracurium	B	+++	Insignificant	++	++	+	0
Cisatracurium	B	+++	Insignificant	++	++	0	0
Pancuronium	S	+	Renal	++	+++	0	++
Vecuronium	S	+	Biliary	++	++	0	0
Rocuronium	S	Insignificant	Biliary	+++	++	0	+
Gantacurium	C	+++	Insignificant	+++	+	+	0

<sup>1</sup>B, benzyloquinolone; S, steroidal; C, chlorofumarate.

<sup>2</sup>Onset: +, slow; ++, moderately rapid; +++, rapid.

<sup>3</sup>Duration: +, short; ++, intermediate; +++, long.

<sup>4</sup>Histamine release: 0, no effect; +, slight effect; ++, moderate effect; +++, marked effect.

<sup>5</sup>Vagal blockade: 0, no effect; +, slight effect; ++, moderate effect.

# **General Pharmacological Characteristics of Non depolarizing NMBA**



# A. Temperature

- Hypothermia prolongs blockade by
- 1.decreasing metabolism
  - (eg, mivacurium, atracurium, and cisatracurium) and
- 2.delaying excretion
  - (eg, pancuronium and vecuronium).

## **B. Acid–Base Balance**

- Respiratory acidosis potentiates the blockade of most nondepolarizing relaxants and antagonizes its reversal.



## C. Electrolyte Abnormalities

- Hypokalemia and hypocalcemia  
.....augment a nondepolarizing block.
- Hypermagnesemia..... potentiates a  
nondepolarizing blockade by competing  
with calcium at the motor end-plate.

# D. Drug interactions

**TABLE 11–4 Potentiation (+) and resistance (–) of neuromuscular blocking agents by other drugs.**

Drug	Effect on Depolarizing Blockade	Effect on Nondepolarizing Blockade	Comments
Antibiotics	+	+	Streptomycin, aminoglycosides, kanamycin, neomycin, colistin, polymyxin, tetracycline, lincomycin, clindamycin
Anticonvulsants	?	–	Phenytoin, carbamazepine, primidone, sodium valproate
Antiarrhythmics	+	+	Quinidine, calcium channel blockers
Cholinesterase inhibitors	+	–	Neostigmine, pyridostigmine
Dantrolene	?	+	Used in treatment of malignant hyperthermia (has quaternary ammonium group)
Inhalational anesthetics	+	+	Volatile anesthetics
Ketamine	?	+	
Local anesthetics	+	+	High doses only
Lithium carbonate	+	?	Prolongs onset and duration of succinylcholine
Magnesium sulfate	+	+	Doses used to treat preeclampsia and eclampsia of pregnancy



# F. Concurrent Disease

- Neurological or muscular disease can have profound effects on an individual's response to muscle relaxants.
- Cirrhotic liver disease and chronic renal failure  
increased volume of distribution and a lower plasma concentration for a given dose of water-soluble drugs, such as muscle relaxants
- Drugs dependent on hepatic or renal excretion may demonstrate prolonged clearance
  - So greater initial (loading) dose—but smaller maintenance dose might be required in these patients.

**TABLE 11-9 Diseases with altered responses to muscle relaxants.**

Disease	Response to Depolarizers	Response to Nondepolarizers
Amyotrophic lateral sclerosis	Contracture	Hypersensitivity
Autoimmune disorders Systemic lupus erythematosus Polymyositis Dermatomyositis	Hypersensitivity	Hypersensitivity
Burn injury	Hyperkalemia	Resistance
Cerebral palsy	Slight hypersensitivity	Resistance
Familial periodic paralysis (hyperkalemic)	Myotonia and hyperkalemia	Hypersensitivity?
Guillain-Barré syndrome	Hyperkalemia	Hypersensitivity
Hemiplegia	Hyperkalemia	Resistance on affected side
Muscular denervation (peripheral nerve injury)	Hyperkalemia and contracture	Normal response or resistance
Muscular dystrophy (Duchenne type)	Hyperkalemia and malignant hyperthermia	Hypersensitivity
Myasthenia gravis	Resistance	Hypersensitivity
Myasthenic syndrome	Hypersensitivity	Hypersensitivity
Myotonia Dystrophica Congenital Paramyotonia	Generalized muscular contractions	Normal or hypersensitivity
Severe chronic infection Tetanus Botulism	Hyperkalemia	Resistance



# **INDIVIDUAL NON-DEPOLARIZING NMBA<sub>s</sub>**

# ATRACURIUM

- Has a quaternary group.
- Benzylisoquinoline structure is responsible for its unique method of degradation.
- It undergoes hofmann elimination and ester hydrolysis.
- Its metabolism is independent of hepatic and renal function.



# Dosage & Storage

**Onset**...2.0 – 3.0 mins

**Intubation**

- 0.5 mg/kg ...intravenously for intubation

**After succinylcholine, intraoperative relaxation can be achieved with**

- 0.25 mg/kg initially, then
- in incremental doses of 0.1 mg/kg every 10–20 min

**infusion**

- 5–10 mcg/kg/min can effectively replace intermittent boluses.

**Storage**

- It must be stored at 2–8°C
- loses 5% to 10% of its potency for each month it is exposed to room temperature.
- At room temperature, it should be used within 14 days

# Side Effects & Clinical Considerations

*Dose-dependent histamine release*  
*...Significant at doses above 0.5 mg/kg.*

## 1. Hypotension and tachycardia

- Unusual unless doses in excess of 0.5 mg/kg
- Transient drop in systemic vascular resistance
- **Prevention**
  - A slow rate of injection minimizes these effects.



## 2. Bronchospasm

- Should be Avoided in asthmatic patients.
- Severe bronchospasm is occasionally seen in patients without a history of asthma

## 3. Laudanosine toxicity

- **Tertiary amine**, is a breakdown product of atracurium's **hofmann elimination**
- Associated with **central nervous system excitation**
- Precipitation of seizures.
- Laudanosine is metabolized by the liver and excreted in urine and bile.



## 4. Temperature and pH Sensitivity

- Hoffman degradation... pH & temperature dependant
- duration of action can be markedly prolonged by hypothermia and to a lesser extent by acidosis.

## 5. Chemical Incompatibility

- Atracurium will precipitate as a free acid if it is introduced into an intravenous line containing an alkaline solution such as thiopental.



## 6. Allergic Reactions

- **Histamine release**....local wheal and flare around the injection site
- **Anaphylactoid reactions** can occur but very rare
- Proposed **mechanisms** include
  - direct immunogenicity
  - acrylate-mediated immune activation.
  - **Reactions to acrylate**, a metabolite of atracurium has also been reported.



# CISATRACURIUM

- It is a stereoisomer of atracurium.
- Four times more potent than atracurium.
- It undergoes hofmann elimination like atracurium but ester hydrolysis does not occur.
- It does not produce the histamine and laudanosine production is 5 times lesser than atracurium.
- Metabolism and elimination are independent of hepatic and renal failure.
- Does **not alter heart rate or blood pressure**, nor does it produce autonomic effects.
- Cisatracurium shares with atracurium the...
  - production of **laudanosine**,
  - **pH and temperature sensitivity** & chemical incompatibility.



# Dosage & Storage

- **Intubating dose** .....0.1–0.15 mg/kg
- Onset of action:2-3 min
- Results in muscle blockade of intermediate duration.
- maintenance **infusion** rate ranges from 1.0–2.0 mcg/kg/min.
- **Refrigeration** (2–8°C)
  - used within 21 days after removal from refrigeration and exposure to room temperature.



# PANCURONIUM

## Physical Structure

- **steroid ring** on which **two modified ACh** molecules are positioned (a bisquaternary relaxant).

## Metabolism & Excretion

- Metabolized (**deacetylated**) by **the liver** to a limited degree.
- Its metabolic products have some neuromuscular blocking activity.
- **Excretion** is primarily **renal (40%)**, although some of the drug is cleared by the **bile (10%)**



## Renal failure.....

- elimination of pancuronium is slowed and neuromuscular blockade is prolonged

## Cirrhosis.....

- may require a **larger initial dose** due to an increased volume of distribution but have reduced maintenance requirements because of a decreased rate of plasma clearance.

## Dosage

- **Intubation dose:** 0.08–0.12 mg/kg of pancuronium provides adequate relaxation in 2–3 min.
- **Intraoperative relaxation** .... 0.04 mg/kg initially followed every 20–40 min by 0.01 mg/kg.

## Storage

- stored at 2–8°C but
- stable for up to 6 months at normal room temperature.



# Side Effects & Clinical Considerations

## A. Hypertension and Tachycardia

- vagal blockade
- sympathetic stimulation.
- catecholamine release from adrenergic nerve endings
- decreased catecholamine reuptake

Large bolus doses of pancuronium should be given with caution to patients in whom an increased heart rate would be particularly detrimental

- (eg, coronary artery disease, hypertrophic cardiomyopathy, aortic stenosis)



## B. Arrhythmias

- **ventricular arrhythmias**...due to
  - Increased atrioventricular conduction and catecholamine release
- Combination of pancuronium, tricyclic antidepressants and halothane are **arrhythmogenic**

## C. Allergic Reactions

- hypersensitive to **bromides** may exhibit allergic reactions to pancuronium (pancuronium bromide).



# VECURONIUM

## Physical Structure

- Pancuronium minus a quaternary methyl group (a monoquaternary relaxant).
- This minor change alters side effects without affecting potency.

## Metabolism & Excretion

- metabolized to a small extent by the liver.

## excretion.....

- primarily on biliary excretion and secondarily (25%) on renal



Long-term administration in ICU.....prolonged neuromuscular blockade (up to several days)

- Due to accumulation of its active 3-hydroxy metabolite and changing drug clearance, resulting in some patients **polyneuropathy**.
- Risk factors- female gender, renal failure, long-term or high-dose corticosteroid therapy and sepsis

Tolerance to non depolarizing muscle relaxants can also develop after long term use.

## Dosage

- equipotent with pancuronium, and the intubating dose is 0.08–0.12 mg/kg.
- maintenance of relaxation--0.04 mg/kg initially followed by increments of 0.01 mg/kg every 15–20 min provides intraoperative relaxation.
- infusion dose: 1–2 mcg/kg/min



**Women** seem to be approximately 30% more sensitive than men to vecuronium, .....(this has also been seen with pancuronium and rocuronium).

- cause .....gender-related differences in fat and muscle mass, protein binding, volume of distribution, or metabolic activity.

## Side Effects & Clinical Considerations

- **1.Cardiovascular**
  - No significant cardiovascular effects.
- **2.Liver Failure**
  - Dependent on biliary excretion,
  - But duration of action of vecuronium is usually not significantly prolonged in patients with cirrhosis unless doses greater than 0.15 mg/kg are given.

# ROCURONIUM

## Physical Structure

- monoquaternary steroid
- analogue of vecuronium

Has rapid onset of action.

6-8 times **less potent** than vecuronium but has approximately the same molecular weight.....

•



## Metabolism & Excretion.....

- **no metabolism** occurs and is eliminated primarily by the **liver** and slightly by the kidneys.

## *Duration of action....*

- prolonged by **severe hepatic failure and pregnancy**
- **Elderly** patients may experience a prolonged duration of action due to decreased liver mass.
- Not significantly affected by renal disease
- **does not have active metabolites**....better choice than vecuronium in the patient requiring prolonged infusions in the intensive care unit.



# Dosage

- For **intubation**.....0.45–0.9 mg/kg intravenously and 0.15 mg/kg boluses for maintenance.
- **Intramuscular** rocuronium (1 mg/kg for infants; 2 mg/kg for children) can be used for intubation after 3–6 min of injection and can be reversed after about 1 hr.
- **Infusion** requirements for rocuronium range from 5–12 mcg/kg/min.



## Side Effects & Clinical Considerations

- Rocuronium (at a dose of 0.9–1.2 mg/kg) has an onset of action that approaches succinylcholine (60–90 s), making it a suitable **alternative for rapid-sequence inductions** but at the cost of a much longer duration of action
- **It is the drug of choice for precurazation.**
- Drug stimulates little **histamine release or cardiovascular disturbance**, although in high doses it has a mild vagolytic property.

# NEWER MUSCLE RELAXANTS



# Gantacurium

New class of nondepolarizing neuromuscular blockers called **chlorofumarates**.

It is provided as a lyophilized powder, because it is not stable as an aqueous solution

**ultrashort duration of action**, similar to that of succinylcholine.

undergoes **nonenzymatic degradation** by two chemical mechanisms:

- rapid formation of **inactive cysteine adduction product** and
- **ester hydrolysis**



## Dosage

- dose of 0.2 mg/kg (ED 95) , the onset of action has been estimated to be 1-2 min, with a duration of blockade similar to that of succinylcholine.

Its clinical duration of action ranged from 5-10 min;

Recovery can be accelerated by

- edrophonium
- exogenous cysteine.

## Cardiovascular effects

- histamine release were observed following the use of three times the ED 95 dosage.



# AV002 (CW002)

Is another investigational nondepolarizing agent.

It is a benzylisoquinolinium fumarate ester-based compound

Intermediate duration of action

metabolism and elimination similar to that of gantacurium.

**Table 29-9 -- Metabolism and elimination of neuromuscular blocking drugs**

Drug	Duration	Metabolism (%)	Elimination		Metabolites
			Kidney (%)	Liver (%)	
Succinylcholine	Ultrashort	Butyrylcholinesterase (98%-99%)	<2%	None	Monoester (succinyl monocholine) and choline; monoester metabolized much more slowly than succinylcholine
Gantacurium	Ultrashort	Cysteine (fast) and ester hydrolysis (slow)	?	?	Inactive cysteine adduction product, chloroformate monoester, and alcohol
Mivacurium	Short	Butyrylcholinesterase (95%-99%)	<5%	None	Monoester and quaternary alcohol. The metabolites are inactive. They are most likely not themselves metabolized any further.
			(Metabolites eliminated in urine and bile)		
Atracurium	Intermediate	Hofmann elimination and nonspecific ester hydrolysis (60%-90%)	10%-40%	None	Laudanosine, acrylates, alcohols, and acids. Although laudanosine has CNS-stimulating properties, the clinical relevance of this effect is negligible.
			(Metabolites eliminated in urine and bile)		
Cisatracurium	Intermediate	Hofmann elimination (77%?)	Renal clearance is 16% of total		Laudanosine and acrylates. Ester hydrolysis of the quaternary monoacrylate occurs secondarily. Because of the greater potency of cisatracurium, laudanosine quantities produced by Hofmann elimination are 5 to 10 times lower than in the case of atracurium, thus making this not an issue in practice.
Vecuronium	Intermediate	Liver (30%-40%)	40%-50%	50%-60%	The 3-OH metabolite accumulates, particularly in renal failure. It has about 80% the potency of vecuronium and may be responsible for delayed recovery in ICU patients.
			(Metabolites excreted in urine and bile, ≈40%)		
Rocuronium	Intermediate	None	10%-25%	>70%	None
Pancuronium	Long	Liver (10%-20%)	85%	15%	The 3-OH metabolite may accumulate, particularly in renal failure. It is about two thirds as potent as the parent compound.
d-Tubocurarine	Long	None	80% (?)	20%	None

CNS, central nervous system; ICU, intensive care unit.



**TABLE 11–7** Clinical characteristics of nondepolarizing muscle relaxants.

Drug	ED <sub>95</sub> for Adductor Pollicis During Nitrous Oxide/Oxygen/Intravenous Anesthesia (mg/kg)	Intubation Dose (mg/kg)	Onset of Action for Intubating Dose (min)	Duration of Intubating Dose (min)	Maintenance Dosing by Boluses (mg/kg)	Maintenance Dosing by Infusion (μg/kg/min)
Succinylcholine	0.5	1.0	0.5	5–10	0.15	2–15 mg/min
Gantacurium <sup>1</sup>	0.19	0.2	1–2	4–10	N/A	—
Rocuronium	0.3	0.8	1.5	35–75	0.15	9–12
Mivacurium <sup>2</sup>	0.08	0.2	2.5–3.0	15–20	0.05	4–15
Atracurium	0.2	0.5	2.5–3.0	30–45	0.1	5–12
Cisatracurium	0.05	0.2	2.0–3.0	40–75	0.02	1–2
Vecuronium	0.05	0.12	2.0–3.0	45–90	0.01	1–2
Pancuronium	0.07	0.12	2.0–3.0	60–120	0.01	—
Pipecuronium <sup>2</sup>	0.05	0.1	2.0–3.0	80–120	0.01	—
Doxacurium <sup>2</sup>	0.025	0.07	4.0–5.0	90–150	0.05	—

<sup>1</sup>Not commercially available in the United States.<sup>2</sup>No longer available in the United States.

# OTHER RELAXANTS

## (Historical interest)

No longer manufactured or not clinically used

### Tubocurarine

- The first muscle relaxant used clinical
- Histamine release
- produce or exacerbate bronchospasm
- often produced hypotension and tachycardia through histamine release
- ability to block autonomic ganglia .
- Tubocurarine is not metabolized significantly,
- elimination is primarily renal and secondarily biliary.



## Metocurine

- shares many of the side effects of tubocurarine
- primarily dependent on renal function for elimination.
- **Patients allergic to iodine** (eg, shellfish allergies) could exhibit hypersensitivity to metocurarine... contain iodide.

## Gallamine

- the **most potent vagolytic** properties of any relaxant,
- entirely dependent on renal function for elimination.

## Alcuronium

- long-acting nondepolarizer
- mild vagolytic properties
- primarily dependent on renal function for elimination

## Rapacuronium

- has a rapid onset of action,
- minimal cardiovascular side effects, and a
- short duration of action.
- withdrawn by the manufacturer following multiple reports of serious **bronchospasm**, Histamine release may have been a factor.



## Decamethonium

- An older depolarizing agent

## Mivacurium

- **Benzylisoquinolinium** derivative,
- Metabolized by pseudocholinesterase
- Duration of action may be prolonged in pathophysiological states that result in low **pseudocholinesterase** levels.
- Intubating dose is 0.2 mg/kg, ... infusion rate being 4-10 mcg/kg/ min.
- **Releases histamine** to about the same degree as atracurium; the
- Cardiovascular effects can be minimized by slow injection.
- Mivacurium is useful particularly for surgical procedures requiring muscle relaxation in which even atracurium and vecuronium seem too long-acting, and when it is desirable to avoid the side-effects of succinylcholine, tonsillectomy
  - E.G. For bronchoscopy, oesophagoscopy, laparoscopy or tonsillectomy



## Doxacurium

- Potent long-acting benzylisoquinolinium compound
- Primarily eliminated by renal excretion.
- Intubating conditions are achieved in 5 min with 0.05 mg/kg.
- Devoid of cardiovascular and histamine-releasing side effects.

## Pipecuronium

- A bisquarternary steroidal compound similar to pancuronium
- Without the vagolytic effects.
- Onset and duration of action are also similar to pancuronium;
- Elimination is primarily through renal (70%) and biliary (20%) excretion.
- Intubating dose ranges from 0.06-0.1 mg/kg

## References:

- Miller's anaesthesia(7<sup>th</sup> edition)
- Clinical anaesthesiology(5<sup>th</sup> edition):Morgan
- Essentials of medical Pharmacology:K.D.Tripathy
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- E-Books





THANK  
YOU