NMBA
Neuromuscular blocking agents

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Skeletal muscle relaxation can be produced by deep inhalational anesthesia, regional nerve block, or neuromuscular blocking agents

muscle relaxation does not ensure unconsciousness, amnesia, or analgesia

In 1942, Harold Griffith published the results of a study using an extract of curare (a South American arrow poison) during anesthesia. Following the introduction of succinylcholine as a “new approach to muscular relaxation,” these agents rapidly became a routine part of the anesthesiologist’s drug arsenal

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.

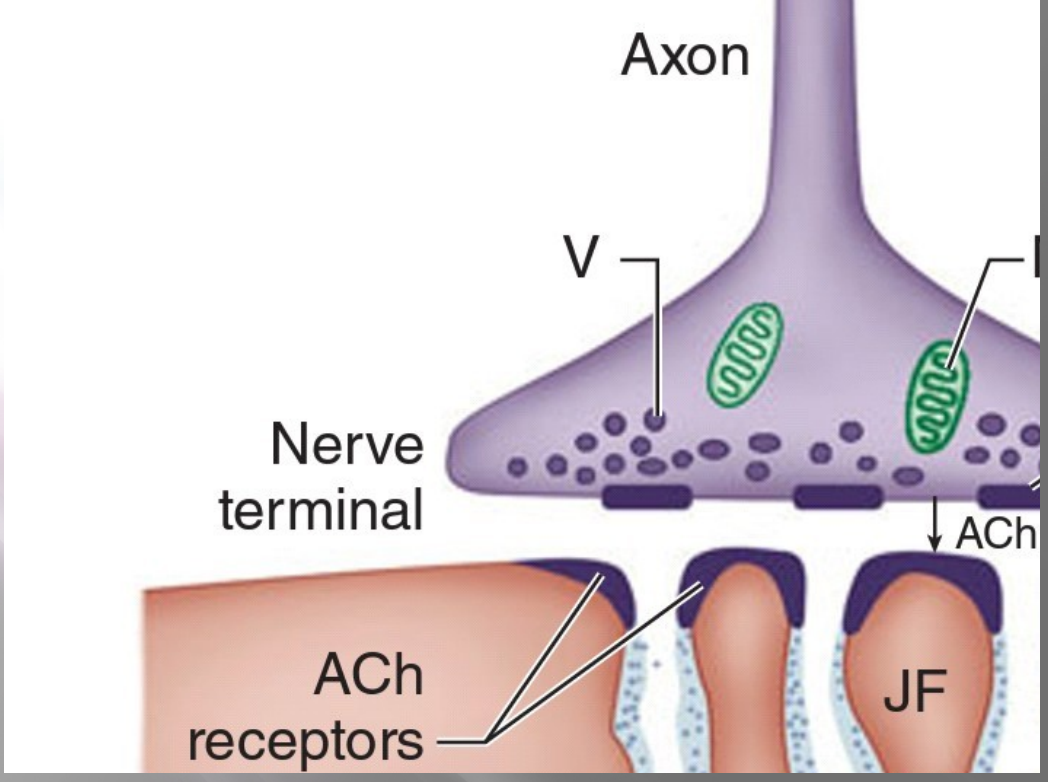
A single vesicle contains about a quantum of Ach (10000 molecules of Ach)

As a nerve's action potential depolarizes the 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


Axon
V
Nerve terminal
ACh
ACh receptors
JF

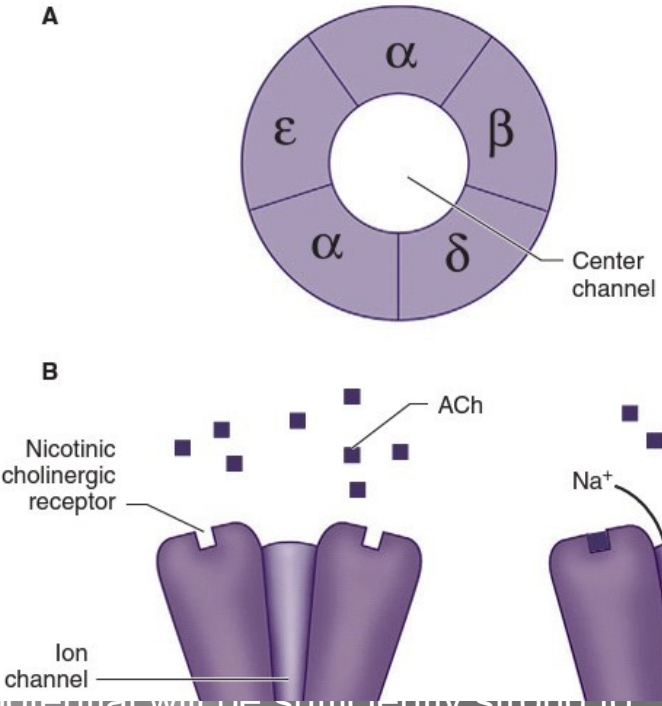


plate potential will be sufficiently strong to

STRUCTURE OF ACH RECEPTORS:

Each ACh receptor in the neuromuscular junction normally consists of five protein subunits; two α subunits; and single β, δ, and ε subunits.

Only the two identical α 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

Sodium channels are present in muscle membrane.

Endplate functional 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.

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.

NMBA are divided into two major groups

- 1. Depolarizing muscle relaxants

  2.Non-Depolarizing muscle relaxants.

- **Distinctions Between Depolarizing & Nondepolarizing Blockade :**
- Neuromuscular blocking agents are divided into two classes: depolarizing and nondepolarizing

all neuromuscular blocking agents are quaternary ammonium compounds whose positively charged nitrogen imparts an affinity to nicotinic ACh receptors

- Whereas most agents have two quaternary ammonium atoms, a few have one quaternary ammonium cation and one tertiary amine that is protonated at physiological pH

- depolarizing muscle relaxants act as ACh receptor agonists, whereas nondepolarizing muscle relaxants function as competitive antago- nists
- depolarizing muscle relaxants very closely resemble ACh and readily bind to ACh receptors, generating a muscle action potential. 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.

- Continuous end-plate depolarization causes muscle relaxation because opening of perijunctional sodium channels is time limited
- After the initial excitation and opening these sodium channels inactivate and 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**
- 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**

Non-classical Blockade

- Some drugs interfere without agonist or antagonist properties
  - Include inhaled anesthetic, local anesthetic or ketamine of unknown mechanisim of its action in blocking the receptor.
  - Interfere with normal functioning of ach binding site and/or opening and closing of receptor channel
  - Closed channel blockade :
    during closed channel blockade, drug physically plugs up the channel preventing passage of cations whether or not Ach has activated the receptor.
  - Open channel blockade:
    - Drug enters and obstructs ach receptor channel after opened

Depolarizing and non-depolarizing Muscle Relaxants

Depolarizing	Non-depolarizing
Short-acting Succinylcholine	Short-acting Mivacurium
	Intermediate-acting
	Atracurium; Cisatracurium
	Rocuronium; Vecuronium
	Long-Acting
	Doxacurium
	Pancuronium; Pipecuronium

Succinylcholine

- Only depolarizing in clinical use
- Copycat Ach structure
- Rapid onset (30-60s)
  - Low lipid solubility as well as relative overdose given
- Short duration of action (< 10 min)
- As it enters the system, most is metabolized by pseudocholinesterase
  - Only small fraction of injected dose reach NMJ

Acetylcholine

Duration of Action: Succinylcholine

- Prolonged by high dose or abnormal metabolism
  - Hypothermia
    - Decreased rate of hydrolysis
  - Low pseudo-cholinesterase levels
    - Pregnancy, liver disease, renal failure and drugs
      - Esmolol, metoclopramide, OCP among others
  - Genetically variable enzyme
    - 1 in 50 = one normal and one abnormal gene
      - Slightly prolonged block (20-30 min)
    - 1 in 3000
      - 2 abnormal genes, up to 4-8 hour blockade
      - Dibucaine resistant –most common abnormal pseudocholinesterase

TABLE 11–3 Drugs known to decrease pseudocholinesterase activity.

Drug	Description
Echothiophate	Organophosphate use for glaucoma
Neostigmine Pyridostigmine	Cholinesterase inhibitors
Phenelzine	Monoamine oxidase inhibitor
Cyclophosphamide	Antineoplastic agent
Metoclopramide	Antiemetic/prokinetic agent
Esmolol	β-Blocker
Pancuronium	Nondepolarizing muscle relaxant
Oral contraceptives	Various agents

Drug Interactions: Succinylcholine

- Cholinesterase inhibitors
  - Prolong phase 1 block
    - Inhibit acetylcholinesterase=higher ach concentration which increase depolarization
    - Reduce hydrolysis of succinylcholine
      - Inhibit pseudocholinestrase

Dosage: Succinylcholine

- Adult
  - Intubation
    - 1-1.5 mg/kg IV *(possibly excessive)
    - .5 mg/kg acceptable if defasciculating dose of non-depolarizer is not used
  - Maintenance
    - Repeated small bolus (10mg) or drip (1g in 500-1000ml titrated to effect)
- Children
  - Intubation
    - Infants/Small kids: 2mg/kg
    - Older children and Adolescents 1mg/kg

Side Effects

- Cardiovascular
  - Variable
    - Secondary to possible stimulation of nicotinic receptors in parasympathetic and sympathetic ganglia, as well as muscarinic receptors in SA node
  - Low doses
    - Can produce negative chronotropic/inotropic effects
  - Higher doses
    - Tend to increase heart rate and contractility as well as elevate circulating catecholamine
  - Children
    - Particularly susceptible to bradycardia
    - Often treated prophylactically with atropine

Side effects cont.

- Fasciculation
  - Signals onset of paralysis
    - Prevented by non-depolarizing relaxant
- Muscle Pains
  - Increased post-op myalgia
    - Possibly from unsynchronized contraction of muscle groups
      - Increased CK and myoglobinemia can be found after succinylcholine given
      - Reduced by NSAID preoperatively

Side Effects

- Hyperkalemia
  - Intubating dose
    - Normal muscle releases potassium to raise serum potassium level by .5 meq/l
  - Excessive hyperkalemia(k level approaching 7meq/l) in cases of
    - Preexisting hyperkalemia (renal failure)
    - Burn Injury
    - Massive Trauma
    - Neurological disorders
    - Many more
  - Cardiac arrest can prove to be quite refractory to routine cardiopulmonary resuscitation

TABLE 11–5 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)

Side effects

- Malignant Hyperthermia
  - Potent triggering agent in patients susceptible to MH
- Intracranial pressure
  - May lead to increase in cerebral blood flow and ICP
    - Attenuated with hyperventilation/good airway control
    - Pre-treat with non-depolarizing muscle relaxant and IV lidocaine 2-3 minutes prior to intubation

Side effects

- Intragastric pressure elevation
  - Abdominal wall fasciculations increase pressure
    - Offset by increase LES tone
    - No increase reflux/aspiration
    - Abolished by pretreatment
- Intraocular pressure elevation
  - Extra-ocular muscle
    - multiple motor-end plates each cell
  - Prolonged depolarization and contraction of muscle transiently raise IOP
    - Worrisome in patient's with injured eye

Non-Depolarizers

Drug	Structure	Metabolism	Primary Excretion	Onset	Duration	Hist. Release	Vagal Blockade
Atracurium	Benzylisoquinolone	+++	x	++	++	+	0
Cisatracurium	Benzylisoquinolone	+++	x	++	++	0	0
Mivacurium	Benzylisoquinolone	Cholinesterase enzymes	x	++	+	+	0
Doxacurium	Benzylisoquinolone	Insignificant	Renal	+++	+++	0	0
Pancuronium	Steroidal	+	Renal	+++	+++	0	++
Pipercuronium	Steroidal	+	Renal	+++	+++	0	0
Vecuronium	Steroidal	+	Biliary	++	++	0	0
Rocuronium	Steroidal	insignificant	Biliary	+	++	0	+

Drug	Intubation dose (mg/kg)	Onset of action for Intubating dose (min)	Duration of action (min)	Maintenance dosing by boluses (mg/kg)	Maintenance dosing by infusion (ug/kg/min)
Succinylcholine	1-1.5	.5-1	5-10	.15	2-15 mg/min
Rocuronium	.6	1.5-2.5	35-75	.15	9-12
Mivacurium	.2	2.5-3.0	15-20	.05	4-15
Atracurium	.5	2.5-3.0	30-45	,1	5-12
Cisatracurium	.2	3-4	40-75	.02	1-2
Vecuronium	.12	2-3	45-90	.01	1-2
Pancuronium	.12	2-3	60-120	.01	x
Pipercuronium	.1	2-3	80-120	.01	x
Doxacurium	.07	4-5	90-150	.05	x

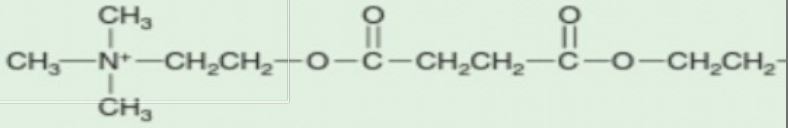
Non-depolarizers

- Three types
  - Benzylisoquinolines
    - Release histamine
  - Steroids
    - Vagolytic

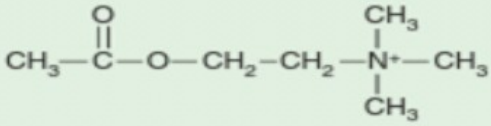
      Related allergic history
  - Other compounds (like chlorofumarates)

Chemical structure of muscle relaxents

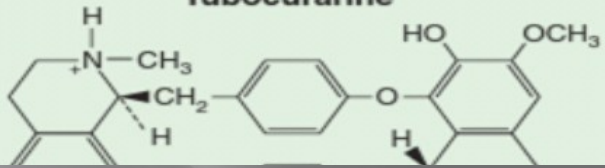
Succinylcholine



Acetylcholine



Tubocurarine



Non-depolarizers

- Intubation
  - None as rapid onset as succinylcholine
  - Quickened by larger dose or priming dose
    - Prolongs duration of blockade and exacerbates SE
  - Priming dose
    - 10-15 % of intubating dose 5 minutes before induction will occupy enough receptors so that paralysis quickly follows full dose
      - Intubation conditions at 60s (Rocuronium)
        - 90s with other intermediate-acting depolarizers
    - Does not usually lead to clinically significant paralysis
      - (75-80% of receptors blocked)
    - Can cause dyspnea, dysphagia and diplopia

Non-depolarizers

- Maintenance relaxation
  - LARGE VARIABLE IN DOSE RESPONSES
  - Requires Close monitoring with Neuro-stimulator
  - Bolus or infusion should be guided by stimulator as well as clinical signs
    - Movement
    - Spontaneous ventilation
  - Some return of neuromuscular transmission should be evident prior to bolus dose
  - Infusion should be titrated at or just above rate that allows return of neuromuscular transmission

Non-depolarizers

- Potentiated by inhalational anesthetics
  - Volatile agents decrease dosage requirements by at least 15 %
  - Depends on agent
    - Des> Sevo > Iso and Enflurane > Halothane > N202
  - Muscle relaxant
    - Pancuronium > vecuronium and atracurium
    - Hypothetically due to volatile induced enhanced affinity for non-depolarizing muscle relaxants

Autonomic side Effects

- Older agents (tubocurarine/metocurine)
  - Blocked autonomic ganglia
    - Decreased contractility/response to hypotension
- Pancuronium
  - Blocks vagal muscarinic receptors
    - Tachycardia
- Newer agents
  - Devoid of significant autonomic effects

Excretion

- Hepatic
  - Pancuronium\Vecuronium metabolized mostly by liver
  - Liver failure
    - Prolongs pancuronium as well as rocuronium blockade
    - Less effect on vecuronium
    - No effect on Cisatracurium or atracurium
- Renal
  - Doxacurium/Pancuronium/Vecuronium and pipecuronium excreted by kidneys
    - Prolonged action in patients with renal failure

Characteristics

- Greater Potency=slower onset
- Temperature
  - Hypothermia prolongs blockade
    - Decreased metabolism and excretion
- Acid-Base
  - Respiratory acidosis
    - Potentiates blockade
- Hypokalemia/Hypocalcemia
  - Prolong blockade
- Hypermagesemia
  - Prolongs blockade by competing with Ca++ at motor end

Age :

- Neonates have an increased sensitivity to nondepolarizing relaxants because of their immature neuromuscular junctions. This sensitivity does not necessarily decrease dosage requirements, as the neonate’s greater extracellular space provides a larger volume of distribution.

Atracurium

- Benzylisoquinoline
  - Metabolized independent of renal and biliary routes
    - Hoffman elimination
  - Triggers dose –dependent histamine release above .5mg/kg (intubating dose)
    - Hypotension/reflex tachycardia/cutaneous flush
  - Laudanosine toxicity
    - Product of breakdown of atracurium
    - CNS excitation: possibly seizures
    - Only relevant at extremely high doses or hepatic failure
  - Precipitate as free acid if placed in IV line with alkaline solution (thiopental)

Cisatracurium

- Stereoisomer of atracurium
- 4 times more potent
- Hoffman elimination
- *Does not produce a dose-dependent increase in histamine
  - Also lower laudaonsine toxicity
- PH/Temperature sensitive
  - Secondary to unique metabolism
  - Prolonged action by hypothermia/acidosis

Mivacurium

- Metabolized by pseudocholinesterase
  - Also prolonged by low pseudocholinesterase levels
- Also causes histamine release
- Brief duration of action
  - About half of atracurium/vec/rocuronium
- Markedly prolonged by prior administration of pancuronium

Doxacuronium

- Benzylisoquinoline
- Renal excretion
  - Similar to other long acting non-depolarizers
- Slow onset (4-6 minutes)
  - .05mg/kg for tracheal intubation within 5 min
- No cardiac or histamine-release side effects
- Duration:60-90 minutes

Pancuronium

- Steroid base
- Primarily renal excretion
  - Slowed by renal failure
- Some excretion by bile
  - Cirrhotic patients require higher initial dose
- Side Effects:
  - HTN and tachycardia
    - Combination of vagal blockade and sympathetic stimulation
      - Caution with CAD, aortic stenosis
  - Arrhythmias
    - Increases AV conduction and catecholamine release
    - Worsened in patients using TCA and halothane

Pipecuronium

- Steroid base (similar to Pancuronium)
- Renal excretion

No cardiovascular side effects

- Advantage over pancuronium

Vecuronium

- Biliary and renal excretion
  - Satisfactory in renal failure however some prolongation occurs
- Side effects
  - No significant CV effects
    - Can cause potentiation of opioid-induced bradycardia
  - *Long term administration causes buildup of active 3-hydroxy metabolite: elongates drug clearance and can cause polyneuropathy

Rocuronium

- Analogue of vecuronium designed for rapid onset
- No active metabolite
  - Better choice for long term infusion
- Can cause prolonged duration of action in elderly
- Primary hepatic and renal elimination
  - Duration of action prolonged by hepatic disease and pregnancy
  - Not Significantly affected by renal failure

Rocuronium

- Useful for quick onset of action
  - Closest non-depolarizer to succinylcholine

  .1 mg/kg shown to be rapid and effective agent (decreased fasciculations and post-op myalgias for precurarization administration of succinylcholine
- Slight vagolytic tendencies

Gantacurium

New class of nondepolari
blockers called chlorofum

It is provided as a lyophili
not stable as an aqueous

Mivacurium demonstrated an ultrashort duration of action, similar to that of succinylcholine. Its pharmacokinetic profile is explained by the fact that it undergoes nonenzymatic degradation by two chemical mechanisms: rapid formation of inactive cysteine adduction product and ester hydrolysis. At a dose of 0.2 mg/kg (ED95), the onset of action has been estimated to be 1-2 min, with a duration of blockade similar to that of succinyl- choline

Its clinical duration of action ranged from 5-10 min; recovery can be accelerated by edropho- nium, as well as by the administration of exogenous cysteine. Cardiovascular effects suggestive of histamine release were observed following the use of three times the ED95 dosage.

TABLE 11–8 Additional considerations in special populations.

Pediatric	Succinylcholine – should not be used routinely Nondepolarizing agents – faster onset Vecuronium – long-acting in neonates
Elderly	Decreased clearance – prolonged duration, except with cisatracurium
Obese	Dosage 20% more than lean body weight; onset unchanged Prolonged duration, except with cisatracurium
Hepatic disease	Increased volume of distribution Pancuronium and vecuronium – prolonged elimination due to hepatic metabolism and biliary excretion Cisatracurium – unchanged Pseudocholinesterase decreased; prolonged action may be seen with succinylcholine in severe disease
Renal failure	Vecuronium – prolonged Rocuronium – relatively unchanged Cisatracurium – safest alternative
Critically ill	Myopathy, polyneuropathy, nicotinic acetylcholine receptor up-regulation

- **REVERSAL OF NEUROMUSCULAR blocking agents :**
- Cholinergic receptors have been subdivided into two major groups :

1.(Nicotinic receptors)Nicotine stimulates the autonomic ganglia and skeletal muscle receptors , 2.(Muscarinic receptors) : muscarine activates end-organ effector cells in bronchial smooth muscle, salivary glands, and the sinoatrial node .

- Both receptors are activated by acetylcholine
- Nicotinic receptors are blocked by muscle relaxants and muscarinic receptors are blocked by anticholinergic drugs, such as atropine.

REVERSAL OF NEUROMUSCULAR blocking agents :

When reversing neuromuscular blockade, the primary goal is to maximize nicotinic transmission with a minimum of muscarinic side effects.

Normal neuromuscular transmission critically depends on acetylcholine binding to nicotinic cholinergic receptors on the motor end-plate. Nondepolarizing muscle relaxants act by competing with acetylcholine for these binding sites, thereby blocking neuromuscular transmission. Reversal of blockade depends on gradual diffusion, redistribution, metabolism, and excretion from the body of the nondepolarizing relaxant (*spontaneous reversal*), often assisted by the administration of specific reversal agents (*pharmacologic reversal*). Cholinesterase inhibitors (

- The increase in acetylcholine caused by cholinesterase inhibitors affects not only the nicotinic receptors of skeletal muscles ,but they can also act at cholinergic muscarinic receptors of several other organ systems, including the cardiovascular and gastrointestinal systems.

Muscarinic side effects of Cholinesterase inhibitors:

Organ System	Muscarinic Side Effects
Cardiovascular	Decreased heart rate, bradyarrhythmias
Pulmonary	Bronchospasm, bronchial secretions
Cerebral	Diffuse excitation[1]
Gastrointestinal	Intestinal spasm, increased salivation
Genitourinary	Increased bladder tone
Ophthalmological	Pupillary constriction

- Unwanted muscarinic side effects are minimized by prior or concomitant administration of anticholinergic medications, such as atropine sulfate or glycopyrolate.
- Atropine has faster onset and shorter duration of action than glycopyrolate.

Succinylcholine is not metabolized by acetylcholinesterase, it unbinds the receptor and diffuses away from the neuromuscular junction to be hydrolyzed in the plasma and liver by another enzyme,

- Sugammadex, a cyclodextrin, is the first selective relaxant-binding agent; it exerts its reversal effect by forming tight complexes in a 1:1 ratio with steroidal nondepolarizing agents (vecuronium, rocuronium,) it does not act on Ach receptors . This drug has been in use in the European Union for the past few years. And FDA approved in the U.S.
- In doses of 2 mg/kg , sugamadex will reverse both rocuronium and vecuronuim from a TOF of 2 to TOF of 0.9 in 2-4 min.

  doses of 4 mg/kg , sugamadex will reverse deeper levels of neuromuscular block to TOF of 0.9 within 2.9 min.
- Immediate reverse from profound block such as that encountered during failed RSI in which mask ventilation

The newer neuromuscular blocking agents, such as gantacurium, which are still under investigation, show promise as ultrashort-acting nondepolar- izing agents; they undergo chemical degradation by rapid adduction with L-cysteine.

Thank you