Muscle Relaxants & Anticholinergic & Cholinesterase inhibitors

- NMJ & Anticholinergic
- Depolarizing Muscle Relaxants
- Non Depolarizing Muscle Relaxants
- Cholinesterase Inhibitors
NMJ, Atropine
Neuromuscular junction

Figure II-2-1. Cholinergic Neuroeffector Junction
a. Ach
b. Norepinephrine, epinephrine, and dopamine
c. Serotonin
d. Histamine
e. Glutamate
f. GABA
g. Glycine
h. Nitric oxide (NO)
Anticholinergic Drugs

- Anticholinergics are drugs that block the action of acetylcholine.
- In normal clinical doses, only muscarinic receptors are blocked by the anticholinergic drugs.
- Used to treat overactive bladder, Parkinson’s disease, diarrhea, vomiting, asthma, chronic obstructive pulmonary disease (COPD), muscle spasms, irritable bowel syndrome (IBS), and other conditions which involve involuntary muscle movement.
- As anticholinergics can affect a variety of functions, including digestion, urination, salivation, and movement, they can help treat many conditions.
- Doctors may also prescribe anticholinergics as muscle relaxants. These drugs can be useful during surgeries too, as they aid relaxation, keep the heartbeat normal, and lower salivation.
Mechanism of action

- They competitively blocks binding by acetylcholine and prevents receptor activation. The cellular effects of acetylcholine, which are mediated through second messengers, are inhibited. The tissue receptors vary in their sensitivity to blockade. In fact, muscarinic receptors are not homogeneous, and receptor subgroups have been identified, including central nervous system (M1,4,5), autonomic ganglia and gastric parietal cells (M1), cardiac (M2), and smooth muscle (M3) receptors.
ATROPINE

- Physical Structure
  - Atropine is a tertiary amine.

- Dosage & Packaging
  - As a premedication, atropine is administered intravenously or intramuscularly in a range of 0.01 to 0.02 mg/kg, up to the usual adult dose of 0.4 to 0.6 mg. Larger intravenous doses up to 2 mg may be required to completely block the cardiac vagal nerves in treating severe bradycardia.

- Clinical Considerations
  - Atropine has particularly potent effects on the heart and bronchial smooth muscle and is the most efficacious anticholinergic for treating bradyarrhythmias.
  - Patients with coronary artery disease may not tolerate the increased myocardial oxygen demand and decreased oxygen supply associated with the tachycardia caused by atropine.
  - A derivative of atropine, ipratropium bromide, is available in a metered-dose inhaler for the treatment of bronchospasm.
The central nervous system effects of atropine are minimal after the usual doses, even though this tertiary amine can rapidly cross the blood–brain barrier.

Atropine has been associated with mild postoperative memory deficits, and toxic doses are usually associated with excitatory reactions.

Atropine should be used cautiously in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder-neck obstruction.

Intravenous atropine is used in the treatment of organophosphate pesticide and nerve gas poisoning.

- **Treatment of acute intoxication:** symptomatic ± physostigmine
Pharmacologic Effects

- Atropine effects in order of increasing dose:
  - Decreased secretions (salivary, bronchiolar, sweat)
  - Mydriasis and cycloplegia
  - Hyperthermia (with resulting vasodilation)
  - Tachycardia
  - Sedation
  - Urinary retention and constipation
  - Behavioral: excitation and hallucinations
**SCOPOLAMINE**

- **Physical Structure**: tertiary amine
- Scopolamine is a more potent antispasmodic than atropine and causes greater central nervous system effects. Clinical dosages usually result in drowsiness and amnesia, although restlessness, dizziness, and delirium are possible.
- The lipid solubility allows transdermal absorption, and transdermal scopolamine (1 mg patch) has been used to prevent postoperative nausea and vomiting.

**GLYCOPYRROLATE**

- **Physical Structure**: Glycopyrrolate is a synthetic product that differs from atropine in being a quaternary amine.
- **Dosage & Packaging**: The usual dose of glycopyrrolate is one-half that of atropine.
- **Clinical Considerations**: Because of its quaternary structure, glycopyrrolate cannot cross the blood–brain barrier and is almost devoid of central nervous system and ophthalmic activity.
- Potent inhibition of salivary gland and respiratory tract secretions is the primary rationale for using glycopyrrolate as a premedication.
- Glycopyrrolate has a longer duration of action than atropine (2–4 h versus 30 min after intravenous administration).
**TABLE 13-1** Pharmacological characteristics of anticholinergic drugs.

<table>
<thead>
<tr>
<th></th>
<th>Atropine</th>
<th>Scopolamine</th>
<th>Glycopyrrolate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Bronchodilatation</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Sedation</td>
<td>+</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Antisialagogue effect</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

1, no effect; +, minimal effect; ++, moderate effect; +++, marked effect.
Neuromuscular Blocking Agents

Depolarizing muscle relaxants and Nondepolarizing muscle relaxants
Objectives

• Different in brief between depolarizing and non depolarizing muscle relaxants.

• Depolarizing muscle relaxants:
  _ structure and mechanism of action
  _ dose, onset and duration of action
  _ indications and contraindications
  _ side effects
  _ factors affecting duration
What’s the difference ......

Depolarizing muscle relaxants act as acetylcholine (ACh) receptor agonists

whereas non_depolarizing muscle relaxants function as competitive antagonists
Source: J.F. Butterworth IV, D.C. Mackey, J. D. Wasnick; Morgan & Mikhail's Clinical Anesthesiology, 6th Edition. Copyright © McGraw-Hill Education. All rights reserved.
Depolarizing muscle relaxants..

* Succinylcholine *
Other name ....

Suxamethonium

*The only depolarizing muscle relaxant in clinical use today.
*Sold under trade names: Anectine, Quelicine, Scoline.
Physical Structure:

consists of two joined Ach molecules:

![Structure of Succinylcholine](structure.png)
Mechanism of action:

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 (sodium channels rapidly “inactivate” with continuing depolarization (fasciculation))...> flaccid paralysis
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.

More prolonged end-plate depolarization can cause poorly understood changes in the ACh receptor that result in a phase II block, which clinically resembles that of nondepolarizing muscle relaxants.

Desensitization (unresponsiveness) then muscle exhaustion & paralysis
* Drug remains binding to Ach receptors causing desensitization till it diffuse away from end plate to plasma

* In plasma it undergo spontaneous hydrolysis by endogenous plasma cholinesterase (pseudocholinesterase)
Metabolism & Excretion:

Succinylcholine remains popular due to its **rapid onset** of action (30–60 s) and **short duration** of action (typically less than 10 min), can be prolonged by high doses, infusion of Succinylcholine, or abnormal metabolism (hypothermia, reduced pseudocholienesterase level which decrease in pregnancy (2–3 min reduction), liver disease, kidney failure, and certain **drug** therapies)

Short duration of action due to metabolization of Succinylcholine by **pseudocholieesterase** into Succinylmonochochine.
<table>
<thead>
<tr>
<th>DRUDS</th>
<th>DISCRIPTIVES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echothiophate</td>
<td>Organophosphate use for glaucoma</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>Cholinesterase inhibitor</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Antineoplastic agent</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Antiemetic</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Beta blocker</td>
</tr>
<tr>
<td>Oral contraceptive</td>
<td></td>
</tr>
</tbody>
</table>
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.
Dosage

The usual adult dose of Succinylcholine for intubation is 1 to 1.5 mg/kg IV

Repeated small boluses (5–10 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 (eg, otolaryngological endoscopies)

The availability of intermediate acting nondepolarizing muscle relaxants has reduced the popularity of Succinylcholine infusions
• dosage requirements for pediatric patients are often greater than for adults.
• Succinylcholine should be stored under refrigeration (2–8°C), and should generally be used within 14 days after removal from refrigeration and exposure to room temperature
Pharmacokinetics:

Administered intravenously (IV)

Due to rapid inactivation by plasma cholinesterase, given by continued infusion
Sequence of paralysis:

short muscles are paralyzed first then later occurs paralysis of other muscles which may lead to death

Finger and orbit muscles   Limbs and trunk muscles   Neck muscles   Intercostals   DIAPHRAGM

Recovery from paralysis occurs in reverse sequence!
Indications:

1- Non Fasting Patients : i.e. Emergency, cesarean section......, (full stomach)  
   **Rapid sequence intubation (RSI)**

2- predicted difficult intubation

3- prior to Electroconvulsive shock therapy (ECT)

4- Operations of short duration where muscle relaxation is needed. (For  
   correction of dislocation and alignment of fractures)

5- For laryngoscopy, bronchoscopy, esophagoscopy
Clinical Contra-indications...

1- inability to maintain airways

2- known allergy / hypersensitivity

3- positive Hx of malignant hyperthermia

4- routine management of children

5- myotonia (M. congenita, M.dystrophica, paramyotonia congenita), why?

6- patient have risk of a hyperkalemic response to succinylcolin .examples

7- lack of resuscitative equipment
Conditions causing susceptibility to Succinylcholine induced hyperkalemia.

- Burn injury
- Massive trauma
- Severe intra abdominal infection
- Spinal cord injury
- Encephalitis
- Stroke
- Guillain–Barré syndrome
- Severe Parkinson disease
- Tetanus
- Prolonged total body immobilization
- Ruptured cerebral aneurysm
- Polyneuropathy
- Closed head injury
- Hemorrhagic shock with metabolic acidosis
- Myopathies (eg, Duchenne dystrophy)
Side effects:

- **Cardiac**: Bradycardia (children & second bolus) / Dysarrythmia / nodal bradycardia / ventricular ectopy / Sinus arrest

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

  Intravenous atropine (0.02 mg/kg in children, 0.4 mg in adults) is normally given prophylactically.

- **Fasciculation**: Visible motor unit contraction, signaled the paralysis by succenylcholine, prevented by pretreatment with a small dose of nondepolarizing relaxant.

- **Hyperkalemia**
Hyperkalemia

• Usually there’s transient & brief increase in serum K+ of about 0.5 meq/L following succinylcholine.

• Pts with K+ >=5.5 meq/L should not receive it.

• Pts having acute disruption of nerve activity of the skeletal muscles if they take this drug they’ll have acute rise in serum K+ to level as high as 13 meq/L → cardiac arrest.

*Tt* : cardiopulmonary resuscitation, requiring calcium, insulin, glucose, bicarbonate and even cardiopulmonary bypass to support the circulation while reducing serum potassium levels.
• **Muscle Pains** – postoperative myalgia (prevented by rocuronium and NSAIDs prior to) / myoglobinemia / increases in serum creatine kinase / myoglobinurea

• **Intragastric Pressure Elevation**

• **Intraocular Pressure Elevation** prevented by pretreatment with a nondepolarizing agent (not always)

• **Masseter Muscle Rigidity** can be a sign of malignant hyperthermia

• **Malignant Hyperthermia**

• **Generalized Contractions**

• **Prolonged Paralysis**

• **Intracranial Pressure** It can also be prevented by pretreating with a nondepolarizing muscle relaxant and administering intravenous lidocaine (1.5–2.0 mg/kg) 2 to 3 min prior to intubation

• **Histamine Release**
non depolarizing drugs
MECHANISM OF ACTION

Nondepolarizing muscle relaxants bind ACh receptors but are incapable of inducing the conformational change necessary for ion channel opening, so prevent depolarization of the muscle cell membrane so inhibiting muscle contraction.

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

Nondepolarizing muscle relaxants act as competitive antagonists. this means that you can overcome their action by increase Ach concentration by giving Ach esterase inhibitors such as pyridostigmine or neostigmine

Neuromuscular blockade occurs even if only one α subunit is blocked.
In contrast to there being only a single depolarizing muscle relaxant, there is a wide selection of nondepolarizing muscle relaxants.

<table>
<thead>
<tr>
<th>Depolarizing</th>
<th>Nondepolarizing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td>Short-acting</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>Mivacurium</td>
</tr>
<tr>
<td></td>
<td>Gantacurium¹</td>
</tr>
<tr>
<td></td>
<td>Intermediate-acting</td>
</tr>
<tr>
<td></td>
<td>Atracurium</td>
</tr>
<tr>
<td></td>
<td>Cisatracurium</td>
</tr>
<tr>
<td></td>
<td>Vecuronium</td>
</tr>
<tr>
<td></td>
<td>Rocuronium</td>
</tr>
<tr>
<td></td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td>Pancuronium</td>
</tr>
</tbody>
</table>

¹Not yet commercially available in the United States.
Based on their chemical structure, they can be classified as benzylisoquinolinium, steroidal, or other compounds

**STRUCTURAL CLASSIFICATION**

- Broadly divided into steroidal compounds and benzylisoquinoline compounds
  - **Steroidal compounds**
    - Pancuronium
    - Vecuronium
    - Pimecuronium
    - Rocuronium
    - Rapacuronium
  - **Benzylisoquinoline compounds**
    - D-tubocurare
    - Metocurine
    - Doxacurium
    - Atracurium
    - Mivacurium
    - Cisatracurium
  - **Others**
    - Gallamine
    - Alcuronium
General Pharmacological Characteristics

Some variables affect all nondepolarizing muscle relaxants.

A. Temperature

HypOthermia prolongs blockade by decreasing metabolism (eg, mivacurium, atracurium, and cisatracurium) and delaying excretion (eg, pancuronium and vecuronium).

B. Acid–Base Balance

Respiratory acidosis potentiates the blockade of most nondepolarizing relaxants and antagonizes its reversal. This could prevent complete neuromuscular recovery in a hypoventilating postoperative patient.
C. Electrolyte Abnormalities

HypOkalemia and hypOcalcemia augment a nondepolarizing block.

The responses of patients with hyperRcalcemia are unpredictable.

HypeRmagnesemia potentiates a nondepolarizing blockade by competing with calcium at the motor end-plate.

D. 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.
E. Additional considerations of muscle relaxants in special populations.

<table>
<thead>
<tr>
<th>Population</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric</td>
<td>Succinylcholine: should not be used routinely</td>
</tr>
<tr>
<td></td>
<td>Nondepolarizing agents: faster onset</td>
</tr>
<tr>
<td></td>
<td>Vecuronium: long-acting in neonates</td>
</tr>
<tr>
<td>Elderly</td>
<td>Decreased clearance: prolonged duration, except with cisatracurium</td>
</tr>
<tr>
<td>Obese</td>
<td>Dosage 20% more than lean body weight; onset unchanged</td>
</tr>
<tr>
<td></td>
<td>Prolonged duration, except with cisatracurium</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Increased volume of distribution</td>
</tr>
<tr>
<td></td>
<td>Pancuronium and vecuronium: prolonged elimination due to hepatic metabolism</td>
</tr>
<tr>
<td></td>
<td>and biliary excretion</td>
</tr>
<tr>
<td></td>
<td>Cisatracurium: unchanged</td>
</tr>
<tr>
<td></td>
<td>Pseudocholinesterase decreased; prolonged action may be seen with succinylcholine in severe disease</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>Vecuronium: prolonged</td>
</tr>
<tr>
<td></td>
<td>Rocuronium: relatively unchanged</td>
</tr>
<tr>
<td></td>
<td>Cisatracurium: safest alternative</td>
</tr>
<tr>
<td>Critically ill</td>
<td>Myopathy, polyneuropathy, nicotinic acetylcholine receptor upregulation</td>
</tr>
</tbody>
</table>
### TABLE 11–3 Potentiation (+) and resistance (−) of neuromuscular blocking agents by other drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Depolarizing Blockade</th>
<th>Effect on Nondepolarizing Blockade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>+</td>
<td>+</td>
<td>Streptomycin, aminoglycosides, kanamycin, neomycin, colistin, polymyxin, tetracycline, lincomycin, clindamycin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>?</td>
<td>−</td>
<td>Phenytoin, carbamazepine, primidone, sodium valproate</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>+</td>
<td>−</td>
<td>Quinidine, calcium channel blockers</td>
</tr>
<tr>
<td>Cholinesterase Inhibitors</td>
<td>+</td>
<td>−</td>
<td>Neostigmine, pyridostigmine</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>?</td>
<td>+</td>
<td>Used in treatment of malignant hyperthermia (has quaternary ammonium group)</td>
</tr>
<tr>
<td>Inhalational anesthetics</td>
<td>+</td>
<td>+</td>
<td>Volatile anesthetics</td>
</tr>
<tr>
<td>Ketamine</td>
<td>?</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>+</td>
<td>+</td>
<td>High doses only</td>
</tr>
<tr>
<td>Lithium carbonate</td>
<td>+</td>
<td>?</td>
<td>Prolongs onset and duration of succinylcholine</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>+</td>
<td>+</td>
<td>Dose used to treat preeclampsia and eclampsia of pregnancy</td>
</tr>
</tbody>
</table>
G. Muscle Groups

The onset and intensity of blockade vary among muscle groups. This may be due to differences in blood flow, distance from the central circulation, or different fiber types. Furthermore, the relative sensitivity of a muscle group may depend on the choice of muscle relaxant.

In general, the diaphragm, jaw, larynx, and facial muscles (orbicularis oculi) respond to and recover from muscle relaxation sooner than the thumb.

Glottic musculature is also quite resistant to blockade, as is often confirmed during laryngoscopy. The dose that produces 95% twitch depression in laryngeal muscles is nearly two times that for the adductor pollicis muscle.
Suitability for Intubation

None of the currently available nondepolarizing muscle relaxants equals succinylcholine’s rapid onset of action or short duration. However, the onset of nondepolarizing relaxants can be quickened by using either a larger dose or a priming dose.

The **ED95** is the dose required to achieve the desired effect in 95% of the population.

For neuromuscular blockers one often specifies the dose that produces 95% twitch depression in 50% of individuals.

Muscle groups vary in their sensitivity to muscle relaxants. For example, the laryngeal muscles—whose relaxation is important during intubation—recover from blockade more quickly than the adductor pollicis.
ATRACURIUM

Physical Structure

Like all muscle relaxants, atracurium has a quaternary group; however, a benzylisoquinoline structure is responsible for its unique method of degradation.

Metabolism & Excretion

Atracurium is so extensively metabolized that its pharmacokinetics are independent of renal and hepatic function, and less than 10% is excreted unchanged by renal and biliary routes.

Two separate processes are responsible for metabolism:
A. **Ester Hydrolysis**
This action is catalyzed by nonspecific esterases, not by acetylcholinesterase or pseudocholinesterase.

B. **Hofmann Elimination** (also known as exhaustive methylation)
A spontaneous nonenzymatic chemical breakdown occurs at physiological pH and temperature.

**Dosage**
A dose of **0.5 mg/kg** is administered intravenously for intubation. After succinylcholine, intraoperative relaxation is achieved with 0.25 mg/kg initially, then in incremental doses of 0.1 mg/kg every 10 to 20 min. An infusion of 5 to 10 mcg/kg/min can effectively replace intermittent boluses.
Side Effects & Clinical Considerations

Atracurium triggers dose-dependent histamine release that becomes significant at doses above 0.5 mg/kg.

A. Hypotension and Tachycardia
Cardiovascular side effects are unusual unless doses in excess of 0.5 mg/kg are administered

B. Bronchospasm
should be avoided in asthmatic patients

C. Laudanosine Toxicity
Laudanosine, a tertiary amine, is a breakdown product of atracurium’s Hofmann elimination and has been associated with central nervous system excitation, precipitation of seizures.
Laudanosine is metabolized by the liver and excreted in urine and bile.

D. Allergic Reactions
CISATRACURIUM

a stereoisomer of atracurium that is four times more potent

Metabolism & Excretion
Like atracurium, cisatracurium undergoes degradation in plasma at physiological pH and temperature by organ-independent Hofmann elimination.

Dosage
Cisatracurium produces good intubating conditions following a dose of 0.1 to 0.15 mg/kg within 2 min.
The typical maintenance infusion rate ranges from 1.0 to 2.0 mcg/kg/min. Thus, it is more potent than atracurium.

Side Effects & Clinical Considerations
Unlike atracurium, cisatracurium does not produce a consistent, dose-dependent increase in plasma histamine levels following administration. Cisatracurium does not alter heart rate or blood pressure, nor does it produce autonomic effects, even at doses as high as eight times ED95.
PANCURONIUM

Metabolism & Excretion
Excretion is primarily renal (40%), although some of the drug is cleared by the bile (10%).

Dosage
A dose of **0.08 to 0.12 mg/kg** of pancuronium provides adequate relaxation for intubation in 2 to 3 min. Intraoperative relaxation is achieved by administering 0.04 mg/kg initially followed every 20 to 40 min by 0.01 mg/kg.

Side Effects
A. Hypertension and Tachycardia: caused by the combination of vagal blockade and sympathetic stimulation.

B. Arrhythmias

C. Allergic Reactions
**VECURONIUM**

Vecuronium is pancuronium minus a quaternary methyl group (a monoquaternary relaxant). This minor structural change beneficially alters side effects without affecting potency.

**Metabolism & Excretion**

It depends primarily on biliary excretion and secondarily (25%) on renal excretion.

Risk factors seem to include female gender, kidney failure, long-term or high-dose corticosteroid therapy, and sepsis.

**Dosage**

Vecuronium is equipotent with pancuronium, and the intubating dose is 0.08 to 0.12 mg/kg.
Women seem to be approximately 30% more sensitive than men to vecuronium, as evidenced by a greater degree of blockade and longer duration of action. The cause for this sensitivity is likely related to gender-related differences in fat and muscle mass and volume of distribution.

Side Effects

A. Cardiovascular
Even at doses of 0.28 mg/kg, vecuronium is devoid of significant cardiovascular effects.

B. Liver Failure
ROCURONIUM
This monoquaternary steroid analogue of vecuronium was designed to provide a rapid onset of action.

Metabolism & Excretion
Rocuronium undergoes no metabolism and is eliminated primarily by the liver and slightly by the kidneys. Its duration of action is not significantly affected by renal disease, but it is modestly prolonged by severe liver failure and pregnancy. Because rocuronium does not have active metabolites, it may be a better choice than vecuronium in the rare patient requiring prolonged infusions in the intensive care unit setting.

Dosage
Rocuronium is less potent than most other steroidal muscle relaxants (potency seems to be inversely related to speed of onset). It requires **0.45 to 0.9 mg/kg** intravenously for intubation and 0.15 mg/kg boluses for maintenance.
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 rapidsequence inductions, but at the cost of a much longer duration of action.
### TABLE 11-5  A summary of the pharmacology of nondepolarizing relaxants.

<table>
<thead>
<tr>
<th>Relaxant</th>
<th>Chemical Structure¹</th>
<th>Metabolism</th>
<th>Primary Excretion</th>
<th>Onset²</th>
<th>Duration³</th>
<th>Histamine Release⁴</th>
<th>Vagal Blockade⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>B</td>
<td>+++</td>
<td>Insignificant</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>B</td>
<td>+++</td>
<td>Insignificant</td>
<td>++</td>
<td>++</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>S</td>
<td>+</td>
<td>Renal</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>S</td>
<td>+</td>
<td>Biliary</td>
<td>++</td>
<td>++</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>S</td>
<td>Insignificant</td>
<td>Biliary</td>
<td>+++</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gantacurium</td>
<td>C</td>
<td>+++</td>
<td>Insignificant</td>
<td>+++</td>
<td>+</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

¹B, benzyllisoquinolone; S, steroidal; C, chlorofumarate.
²Onset: +, slow; ++, moderately rapid; ++++, rapid.
³Duration: +, short; ++, intermediate; ++++, long.
⁴Histamine release: 0, no effect; +, slight effect; ++, moderate effect; ++++, marked effect.
⁵Vagal blockade: 0, no effect; +, slight effect; ++, moderate effect.
Choice of muscle relaxants:

Consideration for choosing a muscle relaxant include:

* Duration of action required
* Route of excretion
* Tendency to release histamine
* Cardiopulmonary side effects
* The ability to reverse the blockage
* Contraindication to any specific muscle relaxant.

*Cost
Role of NMB ‘s in surgery:

• NMB’s are **co-administrated** with anesthetics in the induction phase to induce muscle paralysis
  → **facilitate the surgery**, especially intra-abdominal and intra-thoracic surgeries
  → facilitate **endotracheal intubation**.

• BUT bcz NMB may paralyze muscles required for breathing, **mechanical ventilation** should be available to maintain adequate respiration.
Cholinesterase inhibitors
Ach is the neurotransmitter for the entire parasympathetic, parts of the sympathetic, some neurons in the CNS, and somatic nerves.

**Acetylcholinesterase**
- expressed in neuromuscular junctions & ...
- Acetate + choline

**Cholinergic receptors**
- **nicotinic**
  - Skeletal muscles & ...
- **muscarinic**
  - Smooth muscles, glands & ...

**Cholinesterases**
- **pseudocholinesterase**
  - produced by the liver and found in the plasma
  - responsible for metabolizing succinylcholine, mivacurium & ...

**blockage**
- Depolarizing & non-depolarizing muscle relaxants

**reversal**
- Cholinesterase inhibitors
  - anticholinergic drugs, such as atropine
  - Cholinergic agonists
Cholinesterase inhibition effect

<table>
<thead>
<tr>
<th></th>
<th>Ach</th>
<th>non-depolarizing muscle relaxants except mivacurium</th>
<th>depolarizing muscle relaxants (succinylcholine)</th>
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<tbody>
<tr>
<td>acetylcholinesterase</td>
<td>yes</td>
<td>no</td>
<td>no</td>
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<tr>
<td>pseudoacetylcholinesterase</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

Parasympathetic effects:
- CV: bradycardia
- RS: bronchospasm
- GI: increased activity & secretions
- GU: increased bladder tone
- Eye: miosis

Unwanted muscarinic side effects are minimized by prior administration of anticholinergic drugs, such as atropine.

Administration of cholinesterase inhibitors is controversial for reversing succinylcholine-related apnea in patients who are pseudocholinesterase deficient. The effects may be transient, possibly followed by intensified neuromuscular blockade.

Non-depolarizing muscle relaxants (competitive antagonists) reversed
- Phase 1 (depolarization) augmented
- Phase 2 (desensitization) reversed

Depolarizing muscle relaxants (Ach receptor agonists)
The primary clinical use of cholinesterase inhibitors is to reverse nondepolarizing neuromuscular blockers.

It can be used in the treatment of myasthenia gravis.

Clearance is due to both hepatic metabolism (25–50%) and renal excretion (50–75%). Thus, any prolongation of action of a non-depolarizing muscle relaxant from renal or hepatic insufficiency will probably be accompanied by a corresponding increase in the duration of action of a cholinesterase inhibitor.

The time required to fully reverse a nondepolarizing block depends on several factors, including the choice and dose of cholinesterase inhibitor administered, the muscle relaxant being antagonized, and the extent of the blockade before reversal.

Classified to:

- Reversible: Neostigmine, physostigmine, pyridostigmine, Edrophonium
- Irreversible: Organophosphates (used in pesticides)
NEOSTIGMINE

- Neostigmine displays some limited pseudocholinesterase inhibiting activity, but their effect on acetylcholinesterase is much greater.
- It is lipid insoluble, so it cannot pass through the blood–brain barrier.
- Dose: 0.04 - 0.08 mg/kg (2.5 - 5 mg)
- The effects of neostigmine are usually apparent in 5 min, peak at 10 min, and last more than 1 h.

PYRIDOSTIGMINE
The onset of action is slower (10–15 min) than that of neostigmine, and its duration is slightly longer (>2 h).

PHYSOSTIGMINE
It is lipid soluble and the only clinically available cholinesterase inhibitor that freely passes the BBB.

EDROPHONIUM
the most rapid onset of action (1–2 min) and the shortest duration of effect of any of the cholinesterase inhibitors.