PHARMACOLOGY OF AUTONOMIC NERVOUS SYSTEM

Introduction

The autonomic nervous system regulates functions which are not under voluntary control as the activity of cardiac muscle, smooth muscle and exocrine glands as well as some metabolic processes, e.g. glucose utilization.

The efferent autonomic nerves differ from somatic motor nerves in that unlike the latter, they do not travel directly from the CNS to the structures they innervate, but relay first in synapses (autonomic ganglia) outside the CNS. Thus, each autonomic nerve consists of a preganglionic fibre and a postganglionic one.

Divisions of the Autonomic Nervous System:
Anatomically and physiologically, the autonomic nervous system is subdivided into two parts:
1. Sympathetic division (thoracolumbar outflow) whose preganglionic fibres originate in the lateral horn cells of all thoracic and upper three lumbar segments of the spinal cord. The sympathetic fibres are characterized by having a short preganglionic fibre, the ganglia being mainly in the form of a chain (sympathetic chain) on either side of the vertebral column, and a long postganglionic fibre.

   N.B. The supra renal medulla is a modified sympathetic ganglion.

2. Parasympathetic division (craniosacral outflow) which consists of:
   - Cranial outflow, which originates from certain cranial nuclei, namely III, VII, IX and X.
   - Sacral outflow, which originates from cells in the 2nd, 3rd and 4th sacral segments of the spinal cord.

The parasympathetic fibres are characterized by having a long preganglionic fibre, the ganglia being mainly close to or even embedded in the effector organ, and a short postganglionic fibre.

   N.B. Isolated preparations, as in isolated rabbit's intestine or isolated toad's heart, contain the terminal part of the preganglionic parasympathetic fibre, parasympathetic ganglia and the postganglionic parasympathetic fibre, whereas they only contain the terminal part of the postganglionic sympathetic fibres (no sympathetic ganglia).

Most tissues have dual innervation (sympathetic and parasympathetic) except chromaffin tissue, pilomotor muscle, sweat glands and most blood vessels which possess only sympathetic innervation. The blood vessels which have no parasympathetic supply still have parasympathetic receptors and can respond to acetyl choline.

Physiological Responses:

The two divisions of the autonomic nervous system are usually antagonistic in function e.g. on the heart, bronchioles, GIT wall and sphincters, urinary bladder, etc.; with some exceptions, e.g. both are secretory to the salivary glands and both increase conduction velocity in atria (table 2-1).

Table 2-1: The main effects of the autonomic nervous system
### Pharmacology Of Autonomic Nervous System

#### Sympathetic and Parasympathetic Tones:

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sympathetic Response</th>
<th>Parasympathetic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. SA Node</td>
<td>( \beta_1 ) ↑ HR M</td>
<td>( M_2 ) ↓ HR</td>
</tr>
<tr>
<td>2. Atria</td>
<td>( \beta_1 ) ↑ conductivity M 2</td>
<td>( M_2 ) ↑ conductivity</td>
</tr>
<tr>
<td>3. AV Node</td>
<td>( \beta_1 ) ↑ conductivity M 2</td>
<td>( M_2 ) ↓ conduction velocity (AV block)</td>
</tr>
<tr>
<td>4. Ventricular muscle</td>
<td>( \beta_1 ) ↑ contractility ↑ conductivity ↑ automaticity M 2</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>Blood vessels:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterioles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Sk. muscle</td>
<td>( \beta_2 ) Vasodilatation M 3</td>
<td>No effect</td>
</tr>
<tr>
<td>2. Skin &amp; mucous membranes</td>
<td>( \alpha_1 ) Vasoconstriction M 3</td>
<td>No effect</td>
</tr>
<tr>
<td>Veins</td>
<td>( \alpha_1 ) Vasoconstriction ( \beta_2 ) Vasodilatation</td>
<td>M 3 No effect</td>
</tr>
<tr>
<td>Bronchial Smooth muscle</td>
<td>( \beta_2 ) Relaxation M 3</td>
<td>Contraction</td>
</tr>
<tr>
<td><strong>GIT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Smooth muscle</td>
<td>( \alpha \beta_2 ) ↓ motility M 3</td>
<td>↑ motility</td>
</tr>
<tr>
<td>2. Sphincters</td>
<td>( \alpha_1 ) Contraction M 2, M 3</td>
<td>Relaxation</td>
</tr>
<tr>
<td>3. Glands</td>
<td>- No effect M 3</td>
<td>↑ secretion</td>
</tr>
<tr>
<td><strong>Urinary Bladder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detrusor</td>
<td>( \beta_2 ) Relaxation M 3</td>
<td>Contraction</td>
</tr>
<tr>
<td>Trigone &amp; sphincter</td>
<td>( \alpha_1 ) Contraction M 2, M 3</td>
<td>Relaxation</td>
</tr>
<tr>
<td><strong>Eye</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial muscle</td>
<td>( \alpha_1 ) Contraction (active mydriasis)</td>
<td>-</td>
</tr>
<tr>
<td>Circular muscle</td>
<td>- - M 3</td>
<td>Contraction (Miosis)</td>
</tr>
<tr>
<td>Ciliary muscle</td>
<td>- - M 3</td>
<td>Contraction (accommodation for near vision)</td>
</tr>
<tr>
<td>Male sex organs</td>
<td>( \alpha ) Ejaculation M</td>
<td>Erection</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>( \alpha \beta ) Thick viscous secretion M 3</td>
<td>Profuse watery secretion</td>
</tr>
<tr>
<td>Kidney</td>
<td>( \beta_1 ) Renin secretion -</td>
<td>No effect</td>
</tr>
<tr>
<td>Liver</td>
<td>( \beta_2 ) Glycogenolysis Gluconeogenesis -</td>
<td>No effect</td>
</tr>
</tbody>
</table>
Pharmacology Of Autonomic Nervous System

Under normal resting conditions, some tissues or organs receive continuous flow of impulses along one division of autonomic nervous system, a phenomenon called autonomic tone (sympathetic and parasympathetic tone) e.g. the gastrointestinal wall receives parasympathetic tone keeping the wall in a state of contraction, the blood vessels receive sympathetic tone keeping them in a constricted state, while the constrictor pupillae muscle receives parasympathetic tone keeping the pupil in a constricted state.

Chemical (Neurohumoral) Transmission:

Transmission of nerve impulses from one nerve fibre to another, or from a nerve fibre to an effector organ is mediated through the release of chemical substances (transmitters) from the stimulated nerve ending. Two main chemical transmitters have been identified in autonomic nerves, namely acetyl choline (A.Ch.) and noradrenaline. Nerve fibres which release acetyl choline are called cholinergic fibres and the released acetyl choline acts on cholinergic receptors in the target cells, while nerve fibres which release noradrenaline are called adrenergic (more appropriate noradrenergic) fibres and the released noradrenaline acts on adrenergic receptors. Cholinergic fibres and receptors are further divided into:

a- Central cholinergic fibres and receptors, and
b- Peripheral cholinergic fibres and receptors.

Steps Involved In Neurohumoral Transmission

A- Axonal conduction:

At rest, the interior of the axon is 70 mV negative compared to the exterior. This resting potential is essentially due to higher concentration of $K^+$ ions in the axoplasm, while $Na^+$ and $Cl^-$ ions are present in higher concentrations in the extracellular fluid than in the axoplasm. These ionic gradients are maintained by an energy-dependent pump mechanism, involving adenosine triphosphate (ATP).

In response to a stimulus above the threshold level, a nerve action potential (AP) is initiated. This local reversal of the membrane potential is due to sudden, selective increase in the permeability of the membrane to $Na^+$ ions, which flow rapidly inward, in the direction of their concentration gradient. Repolarization of the membrane follows immediately and results from the rapid replacement of this change by one of increased permeability to $K^+$ ions. These transmembrane ionic currents produce local circuit currents around the axon. By such currents, adjacent inactive regions of the axon are activated and excitation of the next excitable portion of the axonal membrane occurs. This brings about propagation of the AP.

B- Junctional transmission

1- Release of the transmitter:

Neurohumoral transmitters are synthesized in the axonal terminals and stored there within synaptic vesicles. Arrival of nerve action potential [AP] (depolarization) at the axonal terminal causes influx of $Ca^{++}$ at the nerve terminal which promotes fusion of the vesicular and axoplasmic membranes. The contents of the vesicles are then discharged to the exterior by a process called exocytosis.

2- Combination of the transmitter with postjunctional receptors and production of postjunctional potential:
The transmitter diffuses across the synaptic cleft and combines with specialized receptors on the postjunctional membrane. This results in one of two types of permeability changes:

- generalized increase in permeability to cations (mainly Na$^+$) leading to depolarization of the membrane i.e. excitatory postsynaptic potential (EPSP); or
- selective increase in permeability to only the smaller ions (K$^+$ and Cl$^-$) leading to stabilization or hyperpolarization of the membrane i.e. inhibitory postsynaptic potential (IPSP).

3- **Initiation of postjunctional activity:**

If the excitatory postsynaptic potential (EPSP) exceeds a certain threshold value, it initiates a propagated AP in a neuron, a muscle AP in skeletal muscles, or secretion in gland cells, while the inhibitory postsynaptic potential (IPSP) tends to inhibit the effector organ; e.g. acetyl choline causes bradycardia and decreases conduction in the A-V node.

4- **Destruction or dissipation of the transmitter:**

This is achieved by one or both of the following processes:

- Enzymatic destruction: cholinesterase destroys acetyl choline, whereas monoamine oxidase (MAO) and catechol-o-methyl-transferase (COMT) destroy noradrenaline.
- Reuptake of the transmitter by axonal terminals or by tissues: this occurs with noradrenaline at adrenergic endings.
Figure 2-1: Steps involved in excitatory (Ex) and inhibitory (IN) neurohumoral transmission.

1. The nerve action potential (AP), consisting of a self-propagated reversal of negativity (the internal potential, Ei, goes from negative value, through zero potential, indicated by the broken line, to a positive value) of the axonal membrane, arrives at the terminal and causes release of the transmitter.

2. Combination of the excitatory transmitter with postsynaptic receptors (a) produces a localized depolarization, the excitatory postsynaptic potential (EPSP), through an increase in permeability to Na$^+$ or (b) causes a selective increase in permeability to the smaller ions (K$^+$ and Cl$^-$), resulting in a localized hyperpolarization, the inhibitory postsynaptic potential (IPSP).

3. The EPSP initiates a conducted AP in the postsynaptic neuron; this can, however, be prevented by the hyperpolarization induced by a concurrent IPSP.

Cholinergic agonists

Learning Objectives:
By the end of this topic, the student will be able to:
1. Classify cholinergic receptors & drugs acting on them.
2. Define parasympathomimetics and compare between different esters of...
Cholinergic Receptors (Cholinoceptors):

These are receptors which are specifically sensitive to acetylcholine. Depending on their reactivity to certain agonists and antagonists, they are classified into two main types:

1- Nicotinic receptors (Na⁺-channels) (figure 2-2)

Subtypes:

a) $N_N$: found in
   - Autonomic ganglia (both sympathetic & parasympathetic).
   - Suprarenal medulla.
   - Some parts of CNS, e.g. Renshaw cells in spinal cord.

   They are stimulated by acetyl choline and small doses of nicotine, and blocked by ganglion blockers, e.g. hexamethonium.

b) $N_M$: found in neuromuscular junction in skeletal muscle.

   They are stimulated by acetyl choline and anticholinesterases (anti-ChEs), and blocked by neuromuscular blockers, e.g. d-tubocurarine.

Mechanism (transduction): opening of Na⁺ channels leading to depolarization, i.e. EPSP.

2- Muscarinic receptors: (G-protein-coupled) (figure 2-3).

Subtypes:
a) **M₁**: found in:
- Gastric parietal cells and mediates HCl secretion.
- Some neurons in CNS.
- Some autonomic ganglia.
- Some presynaptic sites.

They are stimulated by acetyl choline (EPSP) and blocked by atropine (non-selective) and pirenzepine (selective).

b) **M₂**: found in:
- Heart.
- Smooth muscle.
- Some presynaptic sites.

They are stimulated by acetyl choline and blocked by atropine (non-selective) and gallamine (selective).

c) **M₃**: found in:
- Exocrine glands.
- Smooth muscle.
- Vascular endothelium.

They are stimulated by acetyl choline and blocked by atropine (non-selective).

**Mechanism (transduction):** stimulation of M1 and M3-receptors by acetyl choline leads to stimulation of phospholipase C enzyme which hydrolyses phospholipids in the plasma membrane to give inositol triphosphate (IP₃) and diacyl glycerol (DAG). IP₃ causes the release of intracellular Ca²⁺ from the endoplasmic reticulum, which binds to calmodulin and then activates many intracellular enzymes. Diacyl glycerol activates protein kinase C.

Stimulation of M2-receptors by acetyl choline produces IPSP due to opening of the K⁺ channel (hyperpolarization) and inhibition of adenylate cyclase enzyme (cAMP).
Drugs Acting On Autonomic Receptors

I- Drugs Acting on Adrenergic Receptors:

1. Adrenergic stimulants (sympathomimetic drugs).
2. Adrenergic depressants (sympathetic depressants).
   a) **Adrenergic blockers** (α-blockers, β-blockers, combined α and β-blockers).
   b) **Anti-adrenergics** (sympatholytics): they inhibit sympathetic activity by interfering with the release (adrenergic neuron blocker), formation or storage of catecholamines, but the receptors (α and β) are free and can respond to injected catecholamines.

II. Drugs Acting on Cholinergic Receptors:

1. Drugs acting on peripheral cholinergic (muscarinic) receptors:
   a) **Parasympathomimetics**: they stimulate the peripheral cholinergic receptors (muscarinic).
   b) **Parasympatholytics** (anti-muscarinic drugs, anticholinergic drugs), they block the muscarinic receptors and thus inhibit the muscarinic actions of acetylcholine and other parasympathomimetics.

2. Drugs acting on central cholinergic (nicotinic) receptors:
   a) **Drugs acting on autonomic ganglia (N\textsubscript{2}-receptors):**
- **Ganglion stimulants**: they stimulate the central cholinergic receptors (N_N) in autonomic ganglia.
- **Ganglion blockers**: they block the central cholinergic receptors (N_N) in autonomic ganglia.

b) **Drugs acting on neuromuscular junction (NM-receptors).**
- Neuromuscular blocking agents (N MBA): they interfere with transmission of the nerve impulse at the skeletal neuromuscular junction (one type of skeletal muscle relaxants).
- **Skeletal muscle stimulants.**

**PARASYMPATHOMIMETICS**

They are drugs that stimulate the muscarinic receptors. They include:

**I. Drugs Which Directly Stimulate the Muscarinic Receptors:**

1- Choline esters:
   - a) Acetylcholine (A.Ch.).
   - b) Methacholine.
   - c) Carbachol.
   - d) Bethanechol.

2- Cholinomimetic (naturally-occurring) alkaloids:
   - Pilocarpine.

**II. Drugs Which Indirectly Stimulate the Muscarinic Receptors (Anticholinesterases):**

They inhibit the cholinesterase enzyme thus preventing hydrolysis of acetyl choline leading to its accumulation.

1. Reversible anticholinesterases:
   - a) Physostigmine.
   - b) Neostigmine.
   - c) Neostigmine substitutes.

2. Irreversible anticholinesterases:
   - Organophosphorus compounds.
I- CHOLINE ESTERS

ACETYLCHOLINE

It is the acetic acid ester of choline. Acetyl choline functions as a chemical transmitter at all cholinergic sites in the body (figure 2-4). It is released from:

1- Somatic motor nerve endings, where it is responsible for neuromuscular transmission (N\textsubscript{M}-receptors).
2- Preganglionic sympathetic and parasympathetic nerve endings where it is responsible for ganglionic transmission (N\textsubscript{V}-receptors).
3- Preganglionic nerve to the adrenal medulla (N\textsubscript{V}-receptors).
4- All postganglionic parasympathetic nerve endings (M-receptors).
5- Few postganglionic sympathetic nerve endings e.g. sweat glands and some vasodilator fibres in skeletal muscle (M-receptors).
6- Certain tracts within the C.N.S. (M-receptors).

**Figure 2-4: Sites of action of cholinergic antagonists**

**Acetylcholine Synthesis and Release:**

Acetylcholine is synthesized within nerve terminals in 2 main steps:

- Active transport of choline into the nerve terminal.
- Acetylation of choline by acetyltransferase (Ch.AT) in the presence of acetyl coenzyme A.

\[
\begin{align*}
\text{a- Acetate + Co-A + A.T.P} & \rightarrow \text{Acetyl Co-A + A.D.P.} \\
\text{b- Acetyl Co-A + choline} & \xrightarrow{\text{ChAT}} \text{Acetylcholine + Co-A.}
\end{align*}
\]

Co-enzyme A liberated in reaction (b) is re-used in reaction (a).

Acetylcholine is stored in synaptic vesicles from which it is released by exocytosis in response to a nerve action potential reaching the nerve terminal by calcium entry. Following release in response to
depolarization, acetylcholine diffuses across the synaptic gap to combine with its receptors on the post-synaptic cell. The action is very brief as it is rapidly hydrolyzed (within 1 millisec.) by synaptic true cholinesterase into choline and acetate (figure 2-5).

**Figure 2-5: Acetylcholine synthesis and release**

**Absorption and Fate**

Acetyl choline is ineffective when given orally and should, therefore be given IV. Acetyl choline is rapidly hydrolyzed in the blood and tissues to choline and acetic acid by the cholinesterase enzyme. Two types of cholinesterases participate in the hydrolysis of acetylcholine:

1. **True cholinesterase** which occurs in the CNS, red blood cells and in all cholinergic structures. It is responsible for the hydrolysis of acetyl choline released in the process of cholinergic transmission.
2. **Pseudo-cholinesterase** which occurs in the liver and plasma.
The duration of action of acetylcholine is very short because of its rapid hydrolysis by both enzymes.

The molecule of the cholinesterase enzyme possesses 2 active sites. Attachment of acetylcholine molecule at these 2 sites induces its hydrolysis by the enzyme into choline and acetic acid.

**Pharmacological Actions**

**Acetyl choline has 2 main actions:**

1- **Stimulation of muscarinic receptors**, which occurs chiefly in organs supplied by postganglionic parasympathetic nerves.

2- **Stimulation of nicotinic receptors**, which occurs in:
   a- All autonomic ganglia,
   b- Suprarenal medulla, and
   c- Skeletal muscles.

**A- Muscarine-like effects:**

1- **Cardiovascular system:**
   a) **Heart:**
      - Negative chronotropic action (bradycardia due to slowing of SA node).
      - Negative inotropic action (atria only).
      - Negative dromotropic action (AV-node).
   b) **Blood vessels:** vasodilation indirectly, through the release of endothelium-derived relaxing factor (EDRF) from the intact vascular endothelium. EDRF appears to be nitric oxide (NO). The released NO diffuses to the vascular smooth muscle where it activates guanyl cyclase enzyme and increase cGMP in the smooth muscle, resulting in relaxation.
   c) **Blood pressure:** After IV injection it produces a transient drop in blood pressure due to bradycardia and vasodilatation.

2- **Gastrointestinal tract:** Stimulation of tone, motility and secretion, but the sphincters are relaxed.

3- **Urinary tract:** Stimulation of the detrusor muscle and relaxation of the internal urethral sphincter resulting in evacuation of the bladder.
4- **Bronchioles:** Bronchoconstriction and increased bronchial secretion.

5- **Eye:** Miosis due to stimulation of the constrictor pupillae muscle. The ciliary muscle is also stimulated resulting in accommodation for near vision.

6- **Exocrine glands:** Stimulation of salivary, gastric, bronchial, lachrymal and sweat secretion.

   The muscarinic actions of acetyl choline are stronger than, and even mask its nicotinic actions. The muscarinic actions are blocked by atropine.

**B- Nicotine-like effects:**

1- **Action on autonomic ganglia:** (figure 2-6).

![Figure 2-6: Demonstrates the nicotinic action of acetylcholine on the blood pressure of an anaethesized dog.](image)

The injection of a small dose of acetylcholine in an anaesthetized animal, e.g. dog, produces transient drop in the blood pressure. After atropinization, the effect of small doses of acetylcholine is abolished, but the injection of large doses of acetylcholine produces an increase in blood pressure (Acetyl choline reversal). This rise in blood pressure is due to:

a) **Stimulation of the adrenal medulla** resulting in release of adrenaline and noradrenaline.

b) **Stimulation of sympathetic ganglia** resulting in release of noradrenaline from the postganglionic sympathetic nerves. Stimulation of parasympathetic ganglia would result in release of acetyl choline but it will not be able to stimulate the muscarinic receptors after atropinization.
2- Action on skeletal muscles:

Intra-arterial injection of acetyl choline into an artery supplying a skeletal muscle results in muscle twitches.

The nicotinic actions of acetyl choline at autonomic ganglia are blocked by ganglion blockers, e.g. hexamethonium, but at the neuromuscular junction, they are blocked by neuromuscular blockers e.g. d-tubocurarine.

Therapeutic Uses:

Acetyl choline is only used as an experimental tool. It is not used therapeutically because of its very short duration of action.

SYNTHETIC CHOLINE ESTERS

They include methacholine, carbachol and bethanechol. They have the following advantages over acetylcholine:

i- They have a longer duration of action.
ii- They are effective orally and parenterally.
iii- They are more selective in their actions.

A. Methacholine (used only experimentally)

B- Carbachol

Absorption and Fate

The drug is completely absorbed from GIT and the oral dose is thus nearly equal to the parenteral dose. Carbachol is stable towards hydrolysis by both true and pseudocholinesterase and its effects are consequently unaffected by anticholinesterase.

Pharmacological Actions

Carbachol differs from acetyl choline in the following:

1- It has a longer duration of action.
2- It has muscarinic actions which are more prominent on the eye, gastrointestinal tract and urinary bladder.
3- It has nicotinic actions similar to acetyl choline.
**Therapeutic Uses**

1. Glaucoma: 0.75-3% eye drops.
2. Retention of urine and paralytic ileus: bethanechol is preferred in these cases because of its fewer side effects.

**C- Bethanechol**

**Absorption and Fate**

The drug is completely absorbed from GIT. Similar to carbachol, it is not hydrolyzed by either true or pseudocholinesterase.

**Pharmacological Actions**

It is similar to carbachol, but differs chiefly in having no nicotine actions.

**Therapeutic Uses**

1. Post operative retention of urine.
2. Paralytic ileus.
3. Gastric atony following bilateral vagotomy for peptic ulcer.
4. Glaucoma 1% eye drops.

**N.B. All synthetic choline esters should never be injected IM or IV, and if accidentally given by these routes, atropine is the antidote.**

**Table 2-2:** Shows the main pharmacological differences between the main esters of choline

<table>
<thead>
<tr>
<th>Pharmacological differences between choline esters</th>
<th>Acetylcholine</th>
<th>Carbachol</th>
<th>Bethanechol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption from GIT</td>
<td>Nil</td>
<td>Complete</td>
<td>Complete</td>
</tr>
<tr>
<td>Duration of action</td>
<td>Very short</td>
<td>Longer</td>
<td>Longer</td>
</tr>
<tr>
<td>Hydrolysis by cholinesterase (ChE)</td>
<td>By true and pseudo-ChE</td>
<td>Not hydrolyzed by the true or Pseudo-ChE.</td>
<td></td>
</tr>
<tr>
<td>-Nicotinic actions</td>
<td>***</td>
<td>***</td>
<td>-</td>
</tr>
<tr>
<td>-Muscarinic actions</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>- Specificity of muscarinic actions</td>
<td>-</td>
<td>Eye, G.I.T. and urinary bladder</td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td>IV</td>
<td>Oral or SC</td>
<td></td>
</tr>
</tbody>
</table>
Pharmacology Of Autonomic Nervous System

Contraindications To Choline Esters
1- Bronchial asthma, because they may precipitate severe bronchospasm.
2- Hyperthyroidism, because they may induce atrial fibrillation.
3- Peptic ulcer, because they may increase gastric acid secretion.
4- Coronary insufficiency, because hypotension produced by these drugs further reduces coronary flow.

II- CHOLINOMIMETIC ALKALOIDS

Pilocarpine

Absorption and Fate:
Since it is a tertiary amine, it is readily absorbed from the gastrointestinal tract. It is excreted in urine partly as metabolites and partly unchanged. It is stable to hydrolysis by cholinesterase enzyme.

Mechanism of Action:
It directly stimulates the muscarinic receptors.

Pharmacological Actions:
Its parasympathomimetic effects are chiefly manifested on the following organs:

1- Eye:
When applied locally to the eye, pilocarpine produces:
   a) Miosis.
   b) Spasm of ciliary muscle, leading to accommodation for near vision.
   c) Drop in intraocular pressure as a result of increased drainage of the aqueous humour due to:
      - Contraction of ciliary muscle with consequent opening of the canal of Schlemm.
      - Miosis leading to opening of the spaces of Fontana and widening of the filtration angle.
2- Exocrine glands:
Pilocarpine stimulates sweat (diaphoretic action) and salivary (sialagogue action) secretion in particular, also lacrimal, gastric and bronchial glands are stimulated as well.

3- Smooth muscle:
Pilocarpine stimulates the tone and motility of GIT and causes contraction of the urinary bladder and bronchoconstriction.
All these actions are antagonized by atropine.

Therapeutic Uses
1- Glaucoma: 1-2% pilocarpine nitrate as eye drops. It is the drug of choice in the emergency lowering of intraocular pressure.
2- It counteracts the mydriatic effect of homatropine and eucatropine.
3- It is used in alternation with mydriatics to break mild recent adhesions between the iris and lens.
4- It is used to stimulate salivation in patients who complain of dry mouth during therapy with ganglion blockers.
5- It is added to hair lotions to promote the growth of hair.
6- It is used to treat atropine overdosage.

III- ANTICHOLINESTERASE DRUGS
These drugs inhibit the true and the pseudocholinesterases which hydrolyze acetyl choline, thus higher concentration of this agent is obtained at cholinergic sites where it is released. This leads to prolongation and potentiation of action of the released (accumulated) acetylcholine (figure 2-7).

Anticholinesterases are used in medicine in the treatment of glaucoma and myasthenia gravis. Also, most potent insecticides used in agriculture or for domestic purposes are anticholinesterases. Nerve gases used in chemical war are also anticholinesterases.
Mechanism of Action of Anticholinesterases

1- Reversible anticholinesterases (physostigmine, neostigmine and their substitutes) compete with acetylcholine for the active sites on the true and pseudocholinesterases forming a temporary and loose binding that blocks the entry of acetylcholine and eventually its hydrolysis by the enzyme i.e. act by competitive inhibition at both sites.

2- Irreversible anticholinesterases (organic phosphate esters) initially form a loose, i.e reversible, binding with the enzyme but this eventually becomes firm, leading to permanent inactivation of the enzyme. The body has to replace the inhibited enzyme by synthesizing new enzymes. This replacement takes 2 weeks for the pseudocholinesterase and 3 months for the true cholinesterase.
REVERSIBLE ANTICHOLINESTERASES
PHYSOSTIGMINE (ESERINE) and NEOSTIGMINE (PROSTIGMINE)

Their properties and pharmacology are compared in table 2-3.

<table>
<thead>
<tr>
<th>Source</th>
<th>Physostigmine (Eserine)</th>
<th>Neostigmine (Prostigmine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural alkaloid obtained from the plant “Physostigma venosum” (Calabar beans).</td>
<td>Synthetic.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Physostigmine (Eserine)</th>
<th>Neostigmine (Prostigmine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertiary amine.</td>
<td>Quaternary ammonium compound</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Absorption from G.I.T.</th>
<th>Physostigmine (Eserine)</th>
<th>Neostigmine (Prostigmine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete.</td>
<td>Poor and irregular.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Penetration of lipid barriers.</th>
<th>Physostigmine (Eserine)</th>
<th>Neostigmine (Prostigmine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capable of penetration and can reach the CNS to produce stimulation.</td>
<td>Cannot pass through lipid membranes and so it does not cross the blood brain barrier.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacologic actions</th>
<th>Physostigmine (Eserine)</th>
<th>Neostigmine (Prostigmine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of true and pseudocholinesterase enzymes leading to accumulation of acetyl choline at different sites producing: a- Muscarinic action. b- Nicotinic action. c- CNS stimulation.</td>
<td>Anticholinesterase activity and a direct stimulant action on skeletal muscle. Its muscarinic effects are more marked on the G.I.T. and urinary bladder.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Special effects</th>
<th>Physostigmine (Eserine)</th>
<th>Neostigmine (Prostigmine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locally on the eye it produces: - Miosis - Contraction of the ciliary muscle leading to accommodation for near objects. - Decreased intraocular pressure by the same mechanism as pilocarpine. - Lachrymation. - Twitches of the eye lids (nicotinic action).</td>
<td>Action on skeletal muscle: - Stimulation through inhibition of cholinesterase at the myoneural junction. - Direct stimulant action.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapeutic uses:</th>
<th>Physostigmine (Eserine)</th>
<th>Neostigmine (Prostigmine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used locally for its effects on the eye: 1. Glaucoma. 2. Alternately with mydriatics to break adhesions between the iris and lens. 3. To counteract the mydriatic effect of homatropine and euactropine.</td>
<td>1. Diagnosis and treatment of myasthenia gravis (see text). 2. Antidote to curare. 3. Paralytic ileus. 4. Postoperative urinary retention.</td>
<td></td>
</tr>
</tbody>
</table>
Neostigmine Substitutes

1- Edrophonium (tensilon):
   It has more selective action on the skeletal muscle and a very short duration of action (5 min).

Uses of edrophonium:
   a) Diagnosis of myasthenia gravis. Edrophonium 2 mg I.V. leads to rapid increase in muscle strength. Care must be taken since excess drug (more than 10 mg) may provoke a "cholinergic crisis".
   b) Differentiation between "myasthenic crisis", i.e. exacerbation of myasthenia gravis, and "cholinergic crisis" due to excessive dose of anticholinesterases. Edrophonium (2 mg I.V.) improves myasthenic crisis but worsens cholinergic crisis.
   c) As an antidote to curare.

2- Pyridostigmine is used in the chronic treatment of myasthenia gravis. It has a longer duration of action than neostigmine.

Myasthenia Gravis
   It is an autoimmune disease caused by antibodies to the nicotinic receptors which are stimulated by acetylcholine released at neuromuscular junctions. This causes their degradation, and thus makes fewer receptors available for interaction with the neurotransmitter. Myasthenia gravis is characterized by weakness and rapid fatiguability of skeletal muscles.

Diagnosis of Myasthenia Gravis
   a) 1.5 mg neostigmine preceeded by 0.6 mg atropine (to abolish muscarinic effects) are injected I.M. If muscle weakness improves, this is diagnostic for myasthenia gravis.
   b) Edrophonium: 2 mg I.V.

Treatment of Myasthenia Gravis
   1. Neostigmine tablets: the dose varies according to the severity of the disease from 15-75 mg orally/day. Atropine (0.5-1 mg orally) must be used with neostigmine to counteract the unrequired muscarinic actions such as salivation, flushing,
decreased blood pressure, nausea, vomiting, abdominal pain, diarrhoea and bronchospasm.

2. Neostigmine substitutes: as pyridostigmine.
3. Ephedrine enhances (facilitates) neuromuscular transmission.
4. Immunosuppressive therapy: corticosteroids or cyclophosphamide.
5. Thymectomy in selected cases.

Irreversible Anticholinesterases

Organic phosphates are mainly used as insecticides e.g. parathion, and as war gases, e.g. sarin and tabun. Preparations which are used in therapy include: di-isopropyl-fluoro-phosphate (DFP) which is used as eye drops (0.01-0.1%) in the treatment of glaucoma to produce long lasting miosis, up to one week.

Organic Phosphate Poisoning

Causes
1. Inhalation of sprays or dusts of insecticides.
2. Contamination of skin of agricultural workers.
3. Contamination of crops or food.
4. Accidental or intentional ingestion of insecticides.
5. War gases in the chemical war.

Symptoms
1. Muscarinic effects:
   - Bradycardia and hypotension.
   - Bronchoconstriction and increased bronchial secretion.
   - Excessive sweating, salivation and lacrimation.
   - Miosis.
   - Nausea, vomiting, abdominal cramps and diarrhea.
   - Urinary incontinence.
2. Nicotinic effects:
   - Muscle twitches followed by weakness.
   - Neuromuscular blockade of diaphragm and the intercostal muscles.
3. CNS effects:
• Restlessness, insomnia, tremors and confusion.
• Convulsions and coma.
• Depression of respiratory and cardiovascular centre. Death is usually due to respiratory failure.

**Treatment**

1. Atropine: 2 mg I.V. or I.M. repeated every 5-10 min. till the pupil dilates, and dry mouth and tachycardia occur. Atropine antagonizes the muscarinic effects.

2. Cholinesterase reactivators: oximes e.g. pralidoxime (PAM) and diacetyl monoxime (DAM). The adult dose of pralidoxime is 1-2 g. by I.V. infusion. **Oximes can reactivate the enzyme through:**
   a. They combine with the organophosphorous compound in the already formed organic phosphate-cholinesterase complex, allowing the enzyme to be set free.
   b. They can inactivate any residual inhibitor before it reaches the enzyme.

   **N.B.**
   i. Oximes should be used in association with atropine i.e they are insufficient alone.
   ii. Oximes are effective only in early cases of poisoning. They are ineffective in late cases due to ageing or complete inactivation of enzyme. e.g. DFP ages in 6-8 hours.

3. Anticonvulsants e.g. barbiturates or diazepam.

4. Care of respiration by:
   (a) sucking secretions from respiratory passages and
   (b) artificial respiration.

5. Gastric lavage if taken orally.

6. Contaminated skin should be washed with NaHCO3.
CHOLINERGIC ANTAGONISTS

Learning objectives
By the end of this course, the student will be able to:
1. Differentiate between the antimuscarinic drugs (atropine & hyoscine) in pharmacological actions, side effects and therapeutic uses.
2. Differentiate between synthetic atropine substitutes.
3. Discuss the treatment of acute atropine poisoning.
4. Point to properties of ganglion blockers.
5. Describe the pharmacological actions & kinetics of competitive & depolarizing NMB agents.
6. State the side effects and drug interactions with NMB agents.
7. State lines of treatment of toxicity with NMB agents.
8. List therapeutic uses of NMBAs.
9. Describe mechanisms of inhibition of NM transmission in contrast to antispasticity agents.
10. Discuss the mechanism of action and therapeutic uses of antispasticity agents.

ANTIMUSCARINIC DRUGS

These are drugs that block the muscarinic receptors and thus inhibit the muscarinic actions of acetylcholine and other parasympathomimetics. They generally belong to one of 2 groups:
1. **Natural belladonna alkaloids**: atropine and hyoscine.
2. **Synthetic atropine substitutes**.

They may be also classified according to preferential blockade of muscarinic receptors into:
- **Non-selective muscarinic antagonists** e.g. atropine blocks $M_1$, $M_2$ and $M_3$-receptors.
- **Selective muscarinic antagonists** e.g. selective M1-antagonists include pirenzepine and telenzepine, and selective $M_2$-antagonists as gallamine.
Natural Belladonna Alkaloids

1. Atropine

It is an ester of tropic acid and the base, tropine.

Absorption and Fate

Atropine is absorbed from all sites of administration. It is distributed all over the body, metabolized in liver, but one-third excreted unchanged in urine.

Natural tolerance to atropine is present in certain species e.g. rabbit due to its binding to plasma and tissue proteins and also due the presence of atropinesterase enzyme in their blood and liver, that destroys the alkaloid. In man, however, a mild grade of tolerance might develop after prolonged use e.g. patients with parkinsonism.

Mechanism of Action

Atropine blocks the muscarinic receptors (M1, M2 and M3) by competing with acetylcholine (but it does not affect its release) for them, thereby preventing its binding to these receptors (figure 2-8).

![Figure 2-8: Competition of atropine and scopalamine with acetyl-choline for the muscarinic receptor.](image)

Pharmacological Actions

I- **Parasympathetic depressant action:**

1- **Cardiovascular system:**

   a) **Heart:**

   i. Following I.V. injection, atropine at first produces bradycardia due to stimulation of the cardio-inhibitory centre in the medulla, followed by
tachycardia as a result of blocking the vagal tone to the S.A. node (pace-maker). The extent of tachycardia varies according to the level of the vagal tone e.g. in healthy young adults, in whom the vagal tone is high, atropine produces marked tachycardia, while in children and the elderly (both have low vagal tone) it has relatively a little effect.

ii. Atropine enhances transmission in A.V. node and bundle of His.

**b) Blood vessels and blood pressure:**

Therapeutic doses do not produce a significant action on blood vessels or blood pressure because most vascular beds lack parasympathetic innervation. However, toxic doses in adults and therapeutic doses in children produce cutaneous vasodilatation and flushing of the blush area (atropine flush). This is due to inhibition of sweating, leading to a rise in body temperature (atropine fever).

2- **Gastrointestinal tract:**

a) Reduction of tone and motility of gastrointestinal smooth muscle.

b) Antispasmodic action: atropine relieves intestinal and biliary colics.

c) Reduction of gastric secretion.

3- **Urinary tract:**

a- Ureter: antispasmodic action.

b- Urinary bladder: relaxation of the detrusor muscle and contraction of the sphincter and trigone leading to retention of urine.

4- **Exocrine glands:**

Reduction of salivary, lachrymal, gastric, bronchial and sweat secretion. Reduction of sweat secretion leads to a rise in body temperature (atropine fever) after toxic doses in adults and therapeutic doses in children.

5- **Bronchioles:**

Bronchodilatation and reduction of bronchial secretion.

6- **Eye:**

Local application of atropine in the eye, or its systemic administration produces:

i. Mydriasis due to paralysis of the constrictor pupillae muscle (passive mydriasis).
ii. Paralysis of the ciliary muscle (cycloplegia) leading to loss of accommodation to near objects.

iii. Increased I.O.P. due to closure of the canal of Schlemm and obstruction of the spaces of Fontana.

iv. Loss of the light reflex.

v. Inhibition of lachrymation.

The duration of action of atropine following its local application to the eye is 7-10 days, but when given systemically, it takes only few hours.

**II- Action on the central nervous system:**

Atropine produces both stimulant and depressant actions on CNS:

**a) Stimulant actions:**

i- Therapeutic doses stimulate:

- The cardiovagal center causing bradycardia.
- The respiratory center.

ii- Very large doses stimulate the cerebral cortex leading to restlessness, hallucinations and delirium. This central excitation is followed by depression.

**b) Depressant actions:**

i- Decreased tremors and rigidity in parkinsonism.

ii- Counteracts central excitation of eserine and organo-phosphorus compounds.

iii- Reduces the electric activity of the brain.

**III- Action on sensory nerve endings:**

When atropine is applied locally on the skin, it relieves mild pain due to a local anaesthetic action (local anodyne action). It is therefore added to irritant plasters intended for the treatment of local painful conditions.

**N.B.** *The sensitivity of antimuscarinics drugs varies in different organs. The organs most sensitive to atropine are the salivary, bronchial and sweat glands. Secretion of acid by gastric parietal cells is much less sensitive. Smooth muscles and the heart are intermediate in responsiveness. Thus, small doses of atropine (0.5-1 mg) depress salivary, bronchial and sweat secretion. With larger doses (1-2 mg) the pupil dilates, accommodation is inhibited and tachycardia occurs. Larger doses (2-5 mg) inhibit micturition and reduce tone and motility of G.I.T. Still larger doses (above 5 mg) are required to inhibit gastric acid secretion. Therefore, doses of atropine that depress gastric secretion, also invariably affect salivary secretion, ocular accommodation and micturition.*
Therapeutic Uses

1. Preanaesthetic medication:
   Atropine may be administered (0.5-1 mg IM) half an hour before general anaesthesia in order to:
   a) Decrease salivary and bronchial secretions which are increased with some irritant anaesthetics, e.g. ether.
   b) Protect the heart from excessive vagal tone which occurs with some anaesthetics, e.g. halothane.
   c) Counteract the inhibitory effect of morphine and the anaesthetic on the respiratory centre.

2. Antispasmodic, e.g. in intestinal, biliary and renal colics.

3. Heart block due to myocardial infarction, overdose of digitalis or propranolol.

4. Treatment of severe bradycardia and syncope associated with hyperactive carotid sinus reflex.

5. Hyperhidrosis (excessive sweating).

6. Locally in the eye as eye drops:
   a- To produce mydriasis for fundus examination (other short acting substitutes are preferred for adults and older children. For younger children, the greater efficacy of atropine is sometimes necessary).
   b- To counteract the action of miotics.
   c- In corneal ulcers and iritis to keep the iris pulled away from the lens and thus prevents the formation of adhesions. In addition, it alleviates the local pain to some extent by its local anodyne action.

7. As an antidote to overdosage of parasympathomimetics, e.g. organophosphorus poisoning.

Side Effects

1. Dryness of mouth, blurred vision and tachycardia.

2. Retention of urine may occur in patients with enlarged prostate.

3. Acute glaucoma may be precipitated.

4. In children, cutaneous vasodilatation with flushing of the skin and elevation of body temperature.
Contraindications
1- Old persons, or in those susceptible to glaucoma, as it may precipitate an acute attack of glaucoma.
2- Patients with enlarged prostate, as atropine may precipitate urine retention.
3- Fever.
4- Cardiac patients.
5- Thyrotoxicosis.

Preparations and Doses
Atropine sulphate:
• Orally or by injection 0.5-1 mg.
• Eye drops 1%.

Acute Atropine Poisoning
Symptoms:
1- Parasympathetic depressant symptoms: dry mouth, tachycardia, mydriasis and cycloplegia leading to blurred vision. Decreased sweating may lead to fever.
2- Skin: hot, dry and flushed.
3- CNS: restlessness, excitement and hallucinations followed by CNS depression. The cause of death is respiratory failure.

Treatment:
1- Gastric lavage, if atropine was taken orally.
2- Artificial respiration with oxygen, if respiration is depressed.
3- Ice bags to reduce fever.
4- Parasympathomimetics e.g. pilocarpine or eserine to control the parasympathetic depressant symptoms.

N.B. Either pilocarpine or eserine can pass the blood brain barrier and reverse the central as well as the peripheral signs of muscarinic blockade.
5- Central excitation is controlled by sedatives, but should be used with care, since they may lead to further depression if toxicity is advanced. Paraldehyde may be preferred to barbiturates as it does not inhibit the respiratory centre.
2. Hyoscine (scopolamine)

Hyoscine is chemically related to atropine. The difference between the two drugs are shown in table 2-4.

Table 2-4: Comparison Between Atropine And Hyoscine.

<table>
<thead>
<tr>
<th></th>
<th>Atropine</th>
<th>Hyoscine (Scopolamine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td>An ester of tropic acid and the base tropine</td>
<td>An ester of tropic acid and the base scopine</td>
</tr>
<tr>
<td>Duration of action</td>
<td>Longer</td>
<td>Shorter</td>
</tr>
<tr>
<td>Parasympathetic depressant action pronounced on:</td>
<td>GIT and the heart</td>
<td>Eye and certain exocrine gland (salivary, bronchial and sweat).</td>
</tr>
<tr>
<td>Action on CNS</td>
<td>Both stimulant and depressant actions, but mainly stimulant (see text).</td>
<td>Mainly depressant:</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Depressant action:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Sedation and hypnosis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Amnesia to recent events.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Antimotion sickness action.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Antiparkinsonian action.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Stimulant action:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Respiratory centre stimulation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- May cause excitement in presence of pain or with over-dosage</td>
</tr>
</tbody>
</table>

Therapeutic Uses Of Hyoscine:

1. **Preanaesthetic medication:** Hyoscine is preferred to atropine in preanaesthetic medication because of the following actions:
   i- Depression of CNS.
   ii- Amnesia.
   iii- Stronger antisecretory action.
   iv- Stronger antiemetic action.
   v- It counteracts respiratory depression of morphine and the anaesthetic.

2. **Antispasmodic.**
3. Prophylaxis of motion sickness (figure 2-11).
4. Parkinsonism (synthetic substitutes are preferred).

**Figure 2-11: Scopolamine is an effective antimotion.**

**SYNTHETIC ATROPINE SUBSTITUTES**

1- Mydriatic atropine substitutes.
2- Antisecretory-antispasmodic atropine substitutes.
3- Antiparkinsonian atropine substitutes.
4- Atropine substitutes decreasing urinary bladder activity.
5- Atropine substitutes used in bronchial asthma.

**[1] Mydriatic Atropine Substitutes**

These compounds have been synthesized in order to reduce the duration of action than atropine. They are used locally in the eye.

They include:
1- Homatropine.
2- Eucatropine.
3- Cyclopentolate (Cyclogyl, Mydriate).
4- Tropicamide (Mydriacil).
Homatropine and Eucatropine

The chief differences between atropine, homatropine and eucatropine are shown in table 2-5.

Table 2-5: Comparison between atropine, homatropine and eucatropine

<table>
<thead>
<tr>
<th></th>
<th>Atropine</th>
<th>Homatropine</th>
<th>Eucatropine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of action</td>
<td>7-10 days</td>
<td>24 hrs.</td>
<td>3-4 hrs.</td>
</tr>
<tr>
<td>Concentration</td>
<td>1%</td>
<td>2%</td>
<td>2-5%</td>
</tr>
<tr>
<td>Cycloplegia</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Antagonism by eserine</td>
<td>Not complete</td>
<td>Complete</td>
<td>Complete</td>
</tr>
</tbody>
</table>

Cyclopentolate and Tropicamide

They are used as 0.5-1% eye drops for producing mydriasis and cycloplegia which is more rapid and shorter in duration than homatropine.


1- **Atropine methyl nitrate** (eumydrin):
   - It is more potent parasympatholytic than atropine.
   - It has also a ganglion blocking action.
   - It is used in the conservative treatment of congenital hypertrophic pyloric stenosis in infants. It is given before meals.

2- **Propantheline** (probanthine) and **oxyphenonium** (antrenyl):
   - Both have potent antimuscarinic action.
   - Both have a ganglion blocking action.
   - They are used in the treatment of peptic ulcer (anti-secretory) and colics (antispasmodic).

3- **Hyoscine butyl bromide** (buscopan): In therapeutic doses, it specifically inhibits the tone of visceral smooth muscles. It is used in the treatment of spasms of GIT, bile duct and urinary tract.

**N.B.** It has no antisecretory action, therefore it is not used in the treatment of peptic ulcer.
4- Pirenzepine (gastrozepin):

It is a selective $M_1$-antagonist used in the treatment of peptic ulcer because of its ability to reduce gastric secretion.

Traditionally, all antimuscarinics lower acid production but with relatively high doses which results in side effects. $M_1$-blockers possess the following advantages over non-selective antimuscarinic agents:

1. In therapeutic doses they have no effect on the eye and its accommodation, therefore, may be used in glaucoma.
2. In therapeutic doses they have no effect on the heart, therefore, may be used in cardiac patients.
3. In therapeutic doses they have no effect on micturition, therefore, may be used in patients with enlarged prostate.
4. In therapeutic doses they have no effect on GIT smooth muscles, therefore, they do not slow gastric emptying and do not prolong the exposure of the ulcer bed to acid.
5. They do not cross the blood brain barrier, therefore have no effect on CNS.

**Therapeutic Uses:**

1. Treatment of peptic ulcer (ulcer dyspepsia).
2. Treatment of non-ulcer dyspepsia such as:
   a. Hyperacid irritable stomach.
   b. Gastritis.
   c. Gastric complaints caused by drugs as non-steroidal anti-inflammatory agents (NSAIDs).

**[3] Antiparkinsonian Atropine Substitutes**

They are discussed later in C.N.S. and include: Trihexy phenidyl (Artane), Benztropine (Cogentin), etc...

**[4] Atropine Substitutes Decreasing Urinary Bladder Activity**

Emepronium (cetiprin) is used to reduce bladder motility and increase its capacity in cases of urinary incontinence.
Atropine Substitutes Used in Bronchial Asthma

Ipratropium (atrovent) has a selective bronchodilator action with a diminished effect on bronchial secretion. It is administered by aerosol. It is discussed later in respiratory pharmacology.

DRUGS ACTING ON AUTONOMIC GANGLIA

[A] Ganglion Stimulant

They have no therapeutic value but are of academic interest as useful experimental tools. They produce stimulation of the central cholinergic receptors (in sympathetic and parasympathetic ganglia) by transient depolarization.

They include:
1- Nicotine and lobeline.
2- Acetylcholine and carbachol.

NICOTINE

It is an alkaloid obtained from the leaves of tobacco plant (Nicotiana tabacum).

Absorption and Fate:
It is absorbed from the respiratory tract, buccal, pharyngeal and GIT mucosa and from the intact skin.
80-90% is detoxicated mainly in the liver and detoxication products are excreted by the kidney, lung and sweat. Nicotine is also excreted in the milk of lactating females.

Pharmacological Actions

1- Peripheral nervous system:
It stimulates all autonomic ganglia in small doses (due to transient depolarization), but with large doses the initial stimulation is followed by block (due to persistent depolarization) and failure of impulse transmission across autonomic ganglia.

2- Central nervous system:
   a- Small doses stimulate the CNS producing tremors and with larger doses, tremors are followed by convulsions and then depression.
   b- Small doses stimulate the respiratory centre reflexly. Large doses produce direct stimulation of the respiratory centre followed by depression.

3- Cardiovascular system:
The effects of nicotine are similar to stimulation of the sympathetic nervous system because nicotine:
   i- Stimulates the sympathetic ganglia.
   ii- Stimulates the adrenal medulla.
   iii- Causes the discharge of catecholamines from the sympathetic nerve endings and chromaffin tissues.
   iv- It also activates the chemoreceptors of the carotid and aortic bodies.
All these actions will produce:
a- Vasoconstriction of the blood vessels except the coronary and skeletal vessels which are dilated.
b- Tachycardia.
c- Increased blood pressure and cardiac output.
d- Increased free fatty acids concentration in the blood and increased platelet adhesiveness which may play a role in the pathogenesis of atheroma and thrombosis.

4- Gastrointestinal tract:
The effects of nicotine on G.I.T. are similar to parasympathetic stimulation, i.e. small doses increase tone and motility (diarrhea) of the bowel and stimulate gastric secretion and large doses are followed by a stage of diminished tone and motility (constipation) and inhibition of gastric secretion.

Tolerance:
Tolerance develops to nicotine when taken repeatedly e.g. tobacco smokers. Cross tolerance exists between nicotine and lobeline.

LOBELINE

It is an alkaloid obtained from Lobelia inflata leaves. Its actions are similar to, but less potent than, nicotine.

Therapeutic Uses:
Respiratory stimulant in asphyxia neonatorum. In this condition, 3 mg is injected in the umbilical vein. It acts through stimulation of chemoreceptors in the carotid and aortic bodies producing reflex stimulation of the respiratory centre.

[B] GANGLION BLOCKERS

They block transmission of nerve impulses across autonomic ganglia, whether sympathetic or parasympathetic. After their administration, stimulation of preganglionic fibres is ineffective, but on stimulation of the postganglionic fibres, the effector organ can respond.

a- Depolarizing ganglion blockers:
These are ganglion stimulants given in large doses e.g. nicotine and lobeline. They produce initial stimulation of the central cholinergic receptors in autonomic ganglia followed by persistent depolarization and block.

These ganglion blockers are not used clinically because of the very large doses needed and also blocking is preceded by stimulation which is not required.

Lobeline is only used therapeutically as a respiratory stimulant in asphyxia neonatorum.
b- Competitive (non-depolarizing) ganglion blockers:

These drugs do not produce initial stimulation of the ganglia but act by competing with acetylcholine for the nicotinic receptors in autonomic ganglia and so prevent the released acetylcholine from depolarizing them. Competitive ganglion blockers include:

1. Quaternary ammonium compounds: e.g. hexamethonium (C6).
2. Monosulfonium compounds: Trimetaphan.

General Pharmacological Properties of Competitive Blockers:

The action of these drugs is more manifested on the hyperactive ganglia and thus their actions can be predicted by knowing the dominant tone of the various organs.

1- Action on cardiovascular system:

a) Effect on blood vessels and blood pressure: By blocking the sympathetic ganglia, the sympathetic tone to the arterioles is reduced and consequently vasodilatation and drop of blood pressure occur. The peripheral blood flow in the extremities is consequently increased. Also, pooling of blood in the dilated venules will reduce the venous return, especially in the standing position, consequently the cardiac output drops and blood pressure falls leading to postural hypotension.

b) Effect on heart: tachycardia and decreased cardiac output occur due to block of the parasympathetic ganglia and interference with the vagal tone to the heart. Moreover, after the use of ganglion blockers, adrenergic receptors become more sensitive to catecholamines.

2- Action on eye:

Due to blockade of parasympathetic ganglia, there is mydriasis, cycloplegia and the intraocular tension may rise in the predisposed.

3- Action on gastrointestinal tract:

Due to blockade of parasympathetic ganglia, there is:

- Inhibition of motility of G.I.T.
- Constipation.
- Paralytic ileus may occur.
• Inhibition of gastric secretion.
• Dryness of mouth due to inhibition of salivary secretion.

4- Action on genito urinary system:
Due to blockade of parasympathetic ganglia, there is:
• Difficulty in micturition.
• Urine retention
• Impotence.

5- Action on skin:
Due to blockade of sympathetic ganglia, there is:
• Reduced sweating (cholinergic).
• Peripheral vasodilatation (warm, dry, pink skin).

The actions of ganglion blockers are summarized in table 2-6.

Table 2-6: Chief effects of ganglion blockers.

<table>
<thead>
<tr>
<th>Site</th>
<th>Predominant tone</th>
<th>Effect of ganglion blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterioles</td>
<td>Sympathetic</td>
<td>- Vasodilatation.</td>
</tr>
<tr>
<td></td>
<td>(adrenergic)</td>
<td>- Increased blood flow to extremities.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hypotension.</td>
</tr>
<tr>
<td>Veins</td>
<td>Sympathetic</td>
<td>- Dilatation: decreased venous return.</td>
</tr>
<tr>
<td>Heart</td>
<td>Parasympathetic</td>
<td>- Decreased cardiac output.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tachycardia.</td>
</tr>
<tr>
<td>GIT</td>
<td>Parasympathetic</td>
<td>- Reduced tone and motility.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Constipation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Decreased gastric secretion.</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Parasympathetic</td>
<td>- Urinary retention.</td>
</tr>
<tr>
<td>Eye</td>
<td>Parasympathetic</td>
<td>- Mydriasis and cycloplegia.</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>Sympathetic</td>
<td>- Decreased sweating (anhidrosis).</td>
</tr>
<tr>
<td></td>
<td>(cholinergic)</td>
<td></td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Parasympathetic</td>
<td>- Dry mouth (Xerostomia).</td>
</tr>
<tr>
<td>Genital system (Erection)</td>
<td>Parasympathetic</td>
<td>- Impotence.</td>
</tr>
</tbody>
</table>
Pharmacological Antagonists of Competitive Blockers:

a) Sympathomimetics antagonize the effects of sympathetic ganglion blockade. However, since the response to sympathomimetics is often enhanced after ganglion blockers, their conventional doses should be reduced.

b) Parasympathomimetics antagonize the effects resulting from blockade of parasympathetic ganglia.

TRIMETAPHAN (ARFONAD):

It is a very short acting competitive ganglion blocker and is a histamine liberator. The vasodilator effect of trimetaphan is mostly due to:

a- A ganglionic blocking effect.

b- A histamine like action.

c- A direct vasodilator effect.

Because of its short duration of action, the drug is not used for treating essential hypertension but its main use is to produce controlled hypotension in anaesthesia during plastic and neurosurgery in order to decrease bleeding and in the treatment of hypertensive crises. It is administered by I.V. drip infusion of 1:1000 solution.

Therapeutic Uses of Competitive Ganglion Blockers:

1- Ganglion blockers were widely used in management of hypertension. Because of the development of tolerance to their antihypertensive effect and their numerous side effects, their use in hypertension is now limited.

2- Trimetaphan may be used to produce controlled hypotension during anaesthesia in neuro- and plastic surgery.

SKELETAL MUSCLE RELAXANTS

The steps involved in neuromuscular transmission are in the following successive order:

1. Nerve action potential.

2. Depolarization of the nerve terminal.
3. Acetylcholine release from "synaptic vesicles" in the motor nerve terminal. Calcium ions play an important role in this process.

4. Acetylcholine diffusion through the "junctional cleft" to the motor end plate.

5. Acetylcholine activation of nicotinic receptors on the surface of the motor end plate, resulting in opening the channel and allowing the inflow of sodium into the cell and the efflux of potassium.

6. Depolarization of the motor end plate (end plate potential).

7. Muscle action potential.

8. Muscle contraction.

Meanwhile, the acetylcholine released is hydrolyzed by cholinesterase enzyme, allowing rapid repolarization of the end plate membrane which becomes once again ready to respond to acetylcholine.

**Classification of Skeletal Muscle Relaxants:**

**A- Neuromuscular blocking agents (NMBs):**

These drugs interfere with transmission of the nerve impulse at the neuromuscular junction. They may be classified:

1. **According to their mechanism of action** into competitive or depolarizing neuromuscular blockers.

   (a) **Competitive (non-depolarizing) neuromuscular blockers**: e.g.

   - Curare alkaloids (Tubocurarine).
   - Gallamine (Flaxedil).
   - Pancuronium (Pavulon).
   - Vecuronium (Norcuron).
   - Atracurium (Tracium).

   These drugs compete with acetylcholine for the nicotinic receptors ($N_{M}$) on the motor end plate and thus prevent acetylcholine from depolarizing them leading to transmission failure and muscle paralysis.

   (b) **Depolarizing neuromuscular blockers**: e.g.

   - Succinylcholine (Suxamethonium).
These drugs produce initial stimulation of the nicotinic receptors on the motor end plate which is manifested as muscle fasciculations, followed by persistent (sustained, prolonged) depolarization of the receptors leading to transmission failure, which is manifested as muscle paralysis.

2. **According to their duration of action:**
   a- **Long acting agents** (more than 35 minutes) e.g. d-tubocurarine and pancuronium.
   b- **Intermediate-acting agents** (20-35 minutes) e.g. gallamine, vecuronium and atracurium.
   c- **Short-acting agents** (less than 20 minutes) e.g. succinyl choline.

3. **According to their route of elimination from the body into:**
   a- Agents mainly eliminated **via kidney** e.g. gallamine and pancuronium.
   b- Agents mainly eliminated **via liver** e.g. d-tubocurarine and vecuronium.
   c- Agents eliminated **via plasma cholinesterase enzyme**, e.g., succinylcholine do not depend on the liver or kidney for their elimination.
   d- Agents spontaneously broken down in plasma (Hofmann elimination) e.g. atracurium.

**N.B.**
- Neuromuscular blocking agents contraindicated in kidney disease include those eliminated mainly via the kidney as well as those metabolized by plasma cholinesterase. Patients with renal failure have decreased plasma cholinesterase levels and thus the duration of action of the latter may be prolonged in patients with impaired renal function.
- Neuromuscular blocking agents contraindicated in liver include those eliminated mainly via the liver as well as those metabolized by plasma cholinesterase. The liver is the site of formation of the plasma cholinesterase enzyme. The duration of action of these agents is thus prolonged in patients with impaired liver function.
- Atracurium may be used safely in patients with impaired liver and/or kidney function.

**B. Antispasticity agents (spasmolytics, myotonolytics):**
These are used to decrease spasticity in neurological conditions e.g. low back syndrome due to spinal cord lesions, and rheumatism e.g. due to muscle...
or joint lesions, which give rise to painful muscle spasms. According to their site of action, they are divided into:

1- **Central muscle relaxants:**

Their site of action is the spinal cord and subcortical areas of the brain, inhibiting polysynaptic pathways involved in producing and maintaining muscle spasm of varied etiology. They do not directly relax spastic muscles. They include benzodiazepine derivatives, baclofen and mephenesin.

2- **Direct muscle relaxants:**

They do not act on central synapses or neuromuscular junction. They act directly on skeletal muscles e.g. dantrolene.

### A. NEUROMUSCULAR BLOCKING AGENTS

**Common features:**

- All of them contain one or two quaternary nitrogens, which makes them poorly soluble in lipid and prevents their entry into the CNS. They do not affect consciousness.

- All of them are highly polar and inactive when administered by mouth. They are always administered intravenously.

#### I- Competitive (Non-Depolarizing) Blockers:

**CURARE ALKALOIDS**

Curare is a generic term for the various arrow poisons which have been employed by the South American Indians for killing wild animals.

Crude curare is obtained from various plants. It contains a number of alkaloids, the chief being d-tubocurarine.

**Absorption and Fate:**

Being a quaternary ammonium compound curare is not absorbed from GIT, but is given IV. The drug is mainly, metabolized in the liver and only 1/3 is excreted unchanged in the urine.
Pharmacological Actions:

1- **Competitive neuromuscular blocking action:**

**Mechanism of Action:**

Curare competes with acetylcholine for the nicotinic receptors at the motor end plate \( (N_M) \) and thus blocks the excitatory action (depolarization) of acetylcholine at the myoneural junction leading to paralysis (figure 2-12).

![Figure 2-12: Mechanism of action of competitive neuromuscular blocking drugs.](image)

**Sequence of paralysis:**

1. Small rapidly contracting muscles e.g. of the face, eye and fingers.
2. Muscle of the limbs, neck and trunk.
3. Intercostal muscles.
4. Diaphragm.

Recovery from muscle paralysis occurs in the reverse order to that of their involvement.

*N.B. Death from toxic doses is due to paralysis of the respiratory muscles (intercostal muscles and diaphragm). Sensation and consciousness are not affected (does not cross BBB).*

**Duration of Action:**

A single IV dose produces skeletal muscle paralysis for 30-40 minutes.

2- **Weak ganglion blocking action:**

Large doses of d-tubocurarine are required for blocking autonomic ganglia than those for blocking neuromuscular transmission.

3- **Histamine release:**
This leads to bronchospasm, hypotension, and excessive bronchial and gastric secretion.

As a result of the above actions, a rapid I.V. injection of a large dose of curare may cause hypotension due to:

a- Peripheral vasodilatation due to histamine release.
b- Sympathetic ganglionic blockade.
c- Diminished venous return due to loss of skeletal muscle tone.

4- Central nervous system:

Being a quaternary ammonium compound, curare cannot penetrate the blood brain barrier and thus has no central actions even after large I.V. doses.

Drug Interactions:

A- Synergists:

1. Many inhalational anaesthetics e.g. ether, halothane exert a stabilizing effect on the postjunctional membrane and therefore act synergistically with competitive blockers. Consequently when competitive blockers are employed during anaesthesia with these agents, their doses should be reduced to 1/3-1/2.

2. Some antibiotics, e.g. aminoglycosides as streptomycin, inhibit acetylcholine release from cholinergic nerves by competing with calcium ions. The paralysis could be reversed by administration of calcium ions. They synergize with curare and other competitive blockers, enhancing the blockade.

3. Chlorpromazine produces skeletal muscle relaxation through an action on CNS and not on the neuromuscular-junction.

4. Hypokalaemia.

5. Local anaesthetics e.g. procaine and antiarrhythmic drugs e.g. quinidine (Class I) may block neuromuscular transmission through a stabilizing effect on the nicotinic receptor ion channels.

6. Calcium channel blockers may augment the neuromuscular block since they inhibit muscle contraction itself after depolarization of the motor end plate.
7. **Effect of disease and ageing:**
   - Myasthenia gravis augments the neuromuscular blockade from these drugs.
   - Advanced age is associated with a prolonged duration of action from competitive muscle relaxants, owing to decreased clearance of drugs by the liver and kidneys. Thus their dose should be reduced in elderly patients.

**B- Antagonists:**

Anticholinesterase drugs e.g. neostigmine and edrophonium increase the concentration of acetylcholine at the motor end plate, resulting in reversal of competitive muscle block. This strategy is employed by anaesthesiologists to shorten the duration of neuromuscular block.

**Toxicity:**

An overdose of curare produces:

1. Failure of respiration due to paralysis of respiratory muscles.
2. Hypotension.
3. Histamine release leading to bronchospasm and other sequelae.

**Treatment Of Toxicity:**

1. Artificial respiration with oxygen under positive pressure and maintenance of a patent airway till complete recovery of normal respiration.

2. **Antidotes:**
   - Neostigmine (1-3 mg I.V.) preceded by atropine (0.6-1.2 mg). Atropine is used to block the undesired muscarinic effects of neostigmine. They are not given I.V. simultaneously since atropine causes transient vagal stimulation before blocking the vagus. This may enhance the effect of neostigmine on the heart resulting in marked bradycardia. Therefore, atropine must be given few minutes before neostigmine. Another precaution that should be considered is that overdosage of neostigmine can lead to increased concentrations of acetylcholine at the motor end pate which can cause muscle paralysis due to a depolarization block.
b- Edrophonium (10 mg IV) which may be repeated if required, since it has a short duration of action.

3- Histamine-receptor antagonists (H₁ and H₂-blockers) to counteract the symptoms due to histamine release.

**GALLAMINE (FLAXEDIL)**

It differs from curare (tubarine) in the following:

1- It is a synthetic curare substitute.
2- It has about 1/5 the activity of d-tubocurarine as a neuromuscular blocker.
3- It has a shorter duration of action (intermediate-acting: 20-30 min).
4- It has a much weaker ganglionic blocking activity.
5- It has a much weaker histamine releasing action.
6- It has a selective parasympathetic depressant action, i.e. selective M₂-blocker (previously named atropine-like or vagolytic action) leading to tachycardia. Consequently, it is not used in patients in whom tachycardia may represent a hazard e.g. thyrotoxicosis.
7- It has no effect on blood pressure.
8- Drug interactions are similar to those of curare.
9- It is entirely excreted by the kidney (95-100%) and hence must not be given to patients suffering from renal failure.

**PANCURONIUM (PAVULON)**

1- It is a synthetic compound containing a steroid nucleus separating two quaternary ammonium groups.
2- It is 5 times as potent as d-tubocurarine.
3- It has a slightly longer duration of action (30-45 minutes) than d-tubocurarine.
4- It has no ganglionic blocking activity.
5- It has no histamine releasing action, therefore does not produce hypotension or bronchoconstriction.
6- It has a moderate vagolytic action causing a moderate increase in heart rate.
7- It may cause some rise in blood pressure.
8- Drug interactions are similar to curare.
9- It is excreted mainly in urine (80%).
10- It is a popular long acting relaxant and is the drug of choice in patients susceptible to hyperthermia.

**VECURONIUM (NORCURON)**

1- An analogue of pancuronium.
2- Like pancuronium, vecuronium is 5 times as potent as curare.
3- It has a shorter duration of action (20-35 minutes) than curare.
4- It has no cardiovascular side effects i.e. no ganglion blocking action, no histamine release, therefore no hypotension, and no vagolytic action.
5- Drug interactions are similar to those of curare.
6- It is broken down in liver (75-90%) and is mainly excreted in bile. It should be avoided in patients with liver disease.

**ATRACURIUM (TRACIUM)**

1- It is as potent as tubocurarine as a neuromuscular blocker.
2- It has a shorter duration of action than tubocurarine.
3- It is unique in that it does not depend on the liver or kidney for its elimination, but it is spontaneously broken down in the plasma at the body temperature and pH by enzymatic hydrolysis and by a non-enzymatic chemical process called "Hofmann's degradation". Thus it is non-cumulative. It could be used in patients with either liver and/or kidney disease. In fact, it is the relaxant of choice in fragile patients and in renal failure.
4- It is a weak histamine releaser, but has no effect on autonomic ganglia or on cardiac muscarinic receptors.
5- Drug interactions are similar to curare.
II- Depolarizing neuromuscular blockers:

**SUCCINYLCHOLINE (SUXAMETHONIUM)**

Chemically it is the dicholine ester of succinic acid i.e. contains two molecules of acetylcholine.

**Absorption and Fate**

The presence of 2 quaternary nitrogens, makes succinylcholine poorly soluble in lipid, inactive orally and always given I.V., and cannot enter the CNS. It has a short duration of action due to its rapid hydrolysis by pseudocholinesterase. This occurs in 2 steps:

- Rapid conversion to "succinylmonocholine" which is a much weaker neuromuscular blocker.
- Slower hydrolysis of the initial metabolite, succinylmonocholine to succinic acid and choline both of which are inactive.

**Pharmacological Actions**

1- **Depolarizing neuromuscular blocking action:**

Succinylcholine acts as an ultra-short skeletal muscle relaxant. Relaxation occurs within one minute after a single intravenous dose of 10-50 mg (0.5-1 mg/kg), becomes maximal within two minutes, and disappears within five minutes. Relaxation is preceded by muscle fasciculations and is not antagonized by anticholinesterases. Muscle pain and soreness may follow succinylcholine administration.

**Mechanism of Action**

1. **Depolarizing neuromuscular blockade:**

   **A- Phase I block (depolarization block):**

   Succinylcholine has a similar effect to acetylcholine on the motor end plate receptors (open the sodium channel and cause depolarization of the motor end plate) but instead of producing transient depolarization, it produces prolonged depolarization which is associated with transmission failure. Thus it produces initial stimulation of the muscle which is manifested as fasciculation of the muscle followed by muscle paralysis.
Phase I block is augmented by anticholinesterases. Recovery from phase 1 block depends on washout of the relaxant molecules from the junctional area (which lacks pseudocholinesterase) and their elimination from the body. (figure 2-13).

B- Phase II block (desensitization block):

Phase II block is a possible complication during prolonged I.V. infusion or repeated IV injection of succinylcholine. To reduce this possibility, the total dose of succinylcholine should be limited to 500 mg and the duration of infusion to 60 minutes.

With continued exposure to succinylcholine, the initial motor end plate depolarization decreases and the membrane becomes repolarized, but still cannot be depolarized again by acetylcholine, as long as succinyl choline is present i.e. desensitization to the effects of acetylcholine (figure 2-13). Thus the motor end plate regains its polarized state but the muscle membrane becomes desensitized to the action of acetylcholine, hence the term "desensitization block". During phase II, the block resembles more the competitive type and can be partially reversed by anticholinesterases (neostigmine and edrophonium).

2. Succinylcholine stimulates the nicotinic receptors in sympathetic and parasympathetic ganglia ($N_n$) and the muscarinic receptors ($M_2$) in the SA-node of the heart. Bradycardia is due to direct myocardial action, muscarinic stimulation and ganglionic stimulation.

3. Histamine release, particularly in larger doses.
Figure 2-13: Mechanism of action of depolarizing neuromuscular blockers.

Table 2-7: Shows a comparison between the characteristics of competitive and depolarizing neuromuscular blockers.

<table>
<thead>
<tr>
<th></th>
<th>Competitive</th>
<th>Depolarizing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase I</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>Initial stimulation</strong></td>
<td>Absent</td>
<td>Initial fasciculations</td>
</tr>
<tr>
<td>(fasciculations)</td>
<td></td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Effect of curare</strong></td>
<td>Additive</td>
<td>Antagonistic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Augmented</td>
</tr>
<tr>
<td><strong>Effect of succinyl-choline</strong></td>
<td>Antagonistic</td>
<td>Additives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Augmented</td>
</tr>
<tr>
<td><strong>Effect of anticholine-sterases</strong></td>
<td>Antagonistic</td>
<td>Augmented</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partially Antagonistic</td>
</tr>
<tr>
<td><strong>Rate of recovery</strong></td>
<td>30-60 min.</td>
<td>4-8 min.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 20 min.</td>
</tr>
</tbody>
</table>
Side Effects:

1- Succinylcholine apnoea:
Occasionally succinylcholine produces prolonged apnoea due to lack of normal plasma (pseudo) cholinesterase levels.
This may be the result of:
   a) Genetic abnormality in the enzyme:
      • Its activity may be lower than normal or
      • Abnormal variant of pseudocholinesterase (atypical form of the enzyme) that may be totally unable to split succinylcholine.
   b) Acquired low level of pseudocholinesterase activity occurs in:
      • Severe liver disease.
      • Malnutrition.

Treatment:
1- Artificial respiration until the muscle power returns.
2- Fresh blood or plasma transfusion to restore cholinesterase enzyme level.
3- No specific antidote is available.

2- Bradycardia: which can be prevented by atropine. Pre-medication with atropine is therefore essential.

3- Hyperkalaemia: may occur especially in patients with burns, massive trauma and renal failure. Such patients, respond to succinylcholine by an exaggerated release of potassium from the nicotinic receptors in muscles into the blood. Severe hyperkalaemia may lead to cardiac arrest.

4- Increased intraocular pressure: occurs one minute after injection, becomes maximal at 2-4 minutes and subsides after 5 minutes. It is due to transient dilatation of the choroidal blood vessels as well as to contraction of the extraocular muscles (fasciculation). It is contraindicated in eye surgery, when the anterior chamber is to be opened.

5- Increased intragastric pressure: due to fasciculations of the abdominal muscles. This is more prone to occur in muscular patients leading to regurgitation of gastric contents and the possibility of their aspiration.

6- Post-operative muscle pain: is an important postoperative complaint in patients who have received succinylcholine. Pain is due to damage produced in
the muscles by unsynchronized contractions of adjacent muscle fibres (fasciculations). Muscle fasciculations can be minimized or avoided by giving the drug very slowly or by prior IV small dose of non-depolarizing neuromuscular blocker.

7- **Malignant hyperthermia**: is a rare congenital complication characterized by severe muscle spasm and sudden rise in temperature after succinylcholine or halothane due to release of calcium from the sarcoplasmic reticulum. The condition is treated by I.V. dantrolene which prevents the release of calcium from the sacroplasmic reticulum.

**Administration:**

Succinylcholine is administered in one of two ways:

1- Single IV dose given slowly within 30-60 seconds to produce muscle relaxation of short duration (5 minutes) e.g. intubation.

2- IV infusion: to produce muscle relaxation as long as required.

Atropine premedication is essential before administration of succinylcholine to control any cholinergic symptoms that may develop e.g. bradycardia, salivation and bronchospasm.

**Therapeutic Uses of Neuromuscular Blockers:**

1- Adjuvant in general anaesthesia: To provide adequate muscle relaxation during surgery thus reducing the amount of the general anaesthetic required, the plane of anaesthetic and the anaesthetic hazards.

2- Facilitation of endotracheal intubation, laryngoscopy, bronchoscopy and oesophagoscopy. The drug of choice for these purposes is succinylcholine given as a single IV injection because of its rapid and short duration of action.

3- To prevent coughing and laryngospasm during operations.

4- Prevention of trauma in electroshock therapy of psychiatric disorders: The drug of choice for this purpose is succinylcholine given as a single IV injection because of its short duration of action.
5- Symptomatic treatment of tetanus and other convulsive states as in epilepsy and local anaesthetic toxicity. The drug of choice is d- tubocurarine given as a single IV injection because of its long duration of action.

**N.B.** Tetanus toxin produces convulsions through inhibiting the inter-neural synaptic inhibition mediated by the amino acid glycine.

6- Facilitation of controlled ventilation in chest and heart surgery and in the intensive care units.

**B- Antispasticity agents (Spasmolytics, myotonolytics)**

**Neurotransmitters of inhibitory interneurones include:**

1. **γ-Amino butyric acid (GABA)** is an inhibitory transmitter in the brain and spinal cord. Two types of GABA receptors have been identified: \( \text{GABA}_A \) and \( \text{GABA}_B \). \( \text{GABA}_A \) receptors mediate post-synaptic inhibition by increasing chloride permeability (i.e. opening Cl channels) of the post-synaptic membrane, whereas, \( \text{GABA}_B \) receptors mediate presynaptic inhibition possibly by reducing calcium ion influx, thus reducing the release of excitatory neurotransmitters.

2. **Glycine** is an inhibitory transmitter in the spinal cord. It mediates postsynaptic inhibition possibly by producing hyperpolarization of motor neurons or interneurons of the spinal cord.

**N.B.** Strychnine, a convulsant drug, is a glycine-receptor antagonist i.e. it attenuates the efficiency of interneuronal synaptic inhibition mediated by the amino acid, glycine.

Muscle spasticity is a state of increased skeletal muscle tone due to an imbalance between central (brain) and spinal control of this tone. Antispasticity agents include drugs that can decrease the pathologically increased tone by acting at any site along the neuromuscular regulatory mechanism (except the neuromuscular junction). The chief agents include:
1- Benzodiazepine derivatives e.g. diazepam

**Mechanism of Action:**
Benzodiazepines enhance binding of GABA to GABA\textsubscript{A} receptors which mediate post-synaptic inhibition through hyperpolarization by opening the chloride channels, thus diminishing the effect of excitatory neurotransmitters.

**Therapeutic Uses:**
1- Anxiety states (given orally).
2- Anticonvulsant in status epilepticus (given I.V.).
3- Antispasticity agent (given orally) a dose of 4-20 mg/kg.

2- Baclofen (Lioresal):

**Mechanism of Action:**

a- It is a GABA\textsubscript{B} receptor agonist, thus it produces presynaptic inhibition by reducing calcium ion influx, which in turn reduces the release of excitatory neurotransmitters in the brain and spinal cord. It inhibits mono- and polysynaptic reflexes.

b- It also inhibits release of substance P in the spinal cord reducing pain in patients with spasticity.

**Therapeutic Uses:**
1- Antispasticity agent to treat muscle spasticity associated with spinal cord lesions (given orally 15 mg, twice daily).
2- Some cases of trigeminal neuralgia.

3- Mephenesin (Myanesin):

**Mechanism of Action:**
Skeletal muscle relaxation without inducing sleep or loss of consciousness. The drug acts as a glycine receptor agonist thus increasing the activity of intraspinal inhibitory interneurones where glycine is the transmitter in spinal and supraspinal polysynaptic pathways.

**Therapeutic Uses:**
1- Antispasticity agent to relax skeletal muscles (1-3 gm t.d.s) in:
- neurological spastic states.
- tetanus.
Pharmacology Of Autonomic Nervous System

- muscle spasm associated with trauma, arthritis and myositis.
2- Specific antidote for strychnine (0.5-3 gm IV).

4- **Dantrolene** (Dantrium):

**Mechanism of Action:**
Dantrolene relaxes skeletal muscles by a direct action on the contractile mechanism beyond the neuromuscular junction. It interferes with excitation contraction coupling hindering the release of calcium from the sarcoplasmic reticulum.

**Therapeutic Uses:**
1- Antispasticity agent to treat muscle spasticity associated with spinal cord lesions (given orally in dose of 25-100 mg/day).
2- Malignant hyperthermia which may occur after succinylcholine or halothane administration due to hereditary impairment of the sacroplasmic reticulum to sequester calcium. Prolonged release of calcium leads to massive painful muscle spasm and increased body temperature (1-2 mg/kg IV injection).