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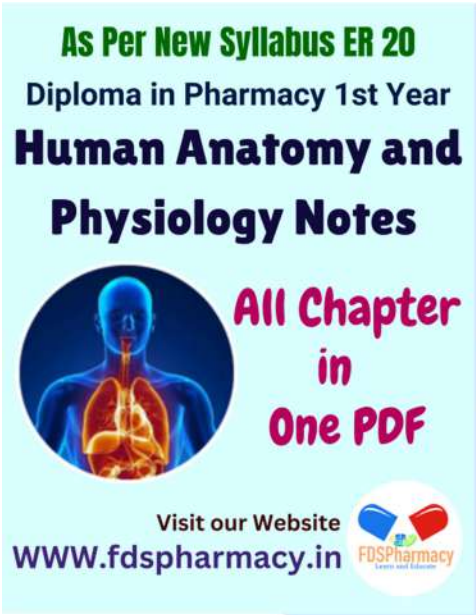
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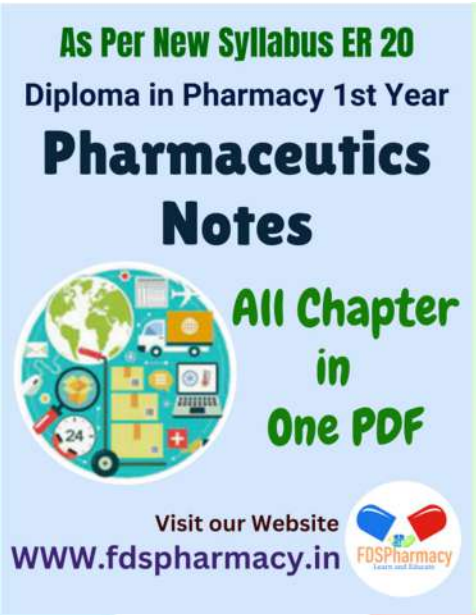
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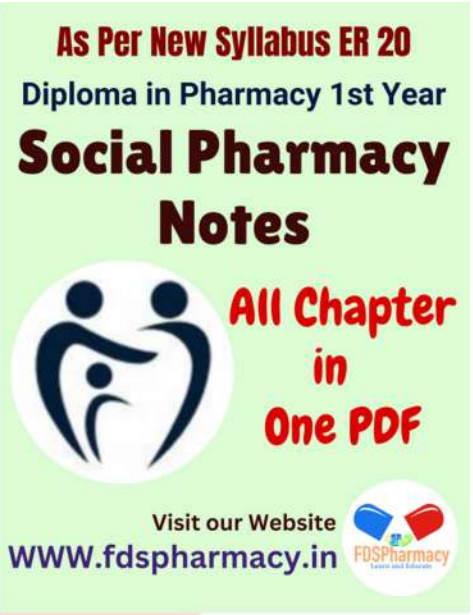
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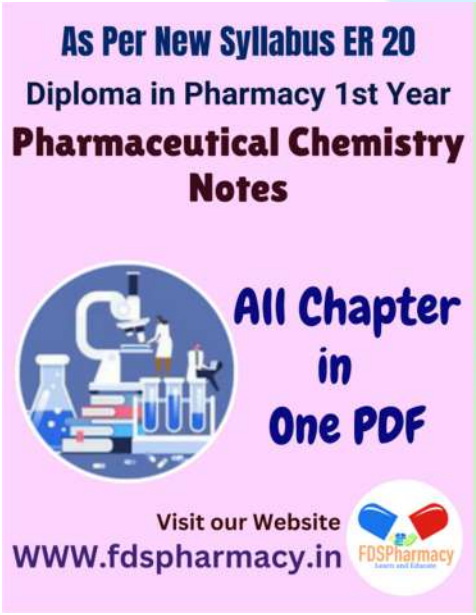
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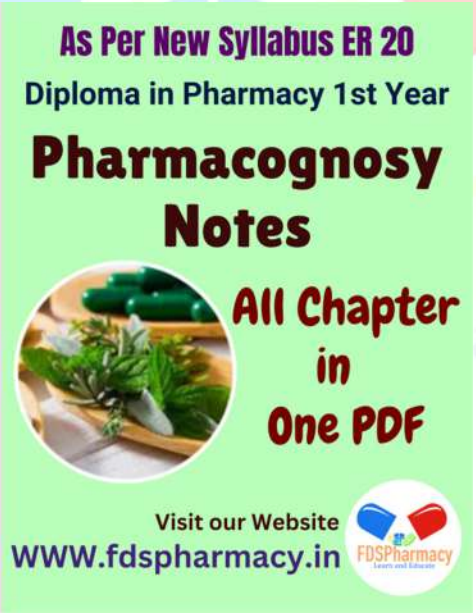
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Link in Description

Diploma in Pharmacy 1st Year
Pharmaceutical Chemistry
Chapter 6 : Drugs Acting on Autonomic Nervous System

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Chapter 6

Drugs Acting on Autonomic Nervous System

SYMPATHOMIMETIC AGENTS (ADRENERGIC AGONISTS)

→ Adrenergic drugs or adrenergic agonists or sympathomimetic agents cause stimulation of the adrenergic receptors in the sympathetic nervous system.
→ They are named so as they mimic the actions of major neurotransmitters of the sympathetic nervous system, i.e., epinephrine and norepinephrine.
→ Adrenergic agents either directly or indirectly stimulate the adrenergic nerves.
→ In direct stimulation, they mimic the actions of noradrenaline; while, indirect stimulation triggers the release of noradrenalinel.
→ The therapeutic application of these drugs is in the treatment of life threatening disorders like acute attacks of bronchial asthma, cardiac arrest, shock, and allergic reactions.
→ These drugs are also used as nasal decongestants and appetite suppressants.

Direct Acting Agents

- The direct acting sympathomimetic agents directly bind and interact to activate the receptor. These agonists may have the property of receptor selectivity where in they can show selectivity (to act) either for any one particular class of receptors (like α- or β-receptors) or for any sub-class (e.g, specificity against β1 or β2 receptors).

The drugs studied below are:

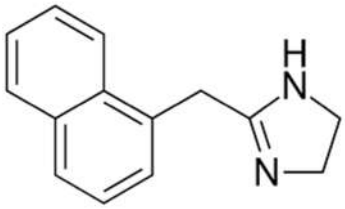
- Nor-epinephrine, *
- Phenylephrine,
- Terbutaline,
- Naphazoline, *
- Epinephrine,
- Dopamine, *
- Salbutamol,
- Tetrahydrozoline.

Naphazoline *

→ Naphazoline acts on ocular arterioles through its rapid sympathomimetic vasoconstrictor action. It decreases the congestion of conjunctiva and is present in many OTC eye drops.

Chemical Name and Structure

- 2-(naphthalen-1-ylmethyl)-4,5-dihydro-1H-imidazole



Mechanism of Action

→ Naphazoline: Naphazoline stimulates alpha-adrenergic receptors in the arterioles of the conjunctiva. Ophthalmic administration causes vasoconstriction of conjunctival blood vessels thereby decreasing conjunctival congestion.

Uses

★ Naphazoline is a decongestant that relieves redness, puffiness, and itchy/watering eyes due to colds, allergies, or eye irritations.

Stability and Storage Conditions

★ The dropper should be stored upright at room temperature between 68°-77°F (20°-25°C) and keep away from moisture and sunlight.

Types of Formulations

- Ophthalmic gel forming solution, Ophthalmic solution

Popular Brand Name

- Privine

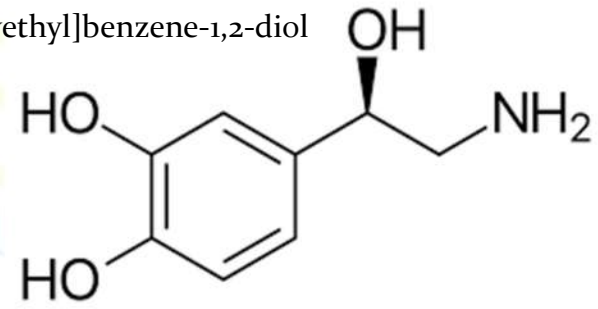
Nor-Epinephrine *

→ Nor-epinephrine (precursor of epinephrine) is a central and autonomic neurotransmitter secreted by adrenal medulla.

→ It acts as a major transmitter for the diffuse projection system which arises from the locus coeruleus of the brain and for the postganglionic sympathetic fibres.

Chemical Name and Structure

- 4-[(1R)-2-amino-1-hydroxyethyl]benzene-1,2-diol



Mechanism of Action

➢ Nor-epinephrine acts on α-adrenergic receptors for peripheral vasoconstriction and on β-adrenergic receptors for causing inotropic stimulation of heart and dilation of coronary arteries.

Uses

★ It maintains blood pressure in acute hypotensive states arising due to Surgical or non-surgical trauma, central vasomotor depression, and haemorhage.

Stability and Storage Conditions

- Solutions of norepinephrine should be stored in PVC bags at 4°C for 61 days with protection from light.

Types of Formulations

♠ Injectable solution, Intravenous solution,

Popular Brand Names

♦ Levarterenol

♦ Levophed

Epinephrine

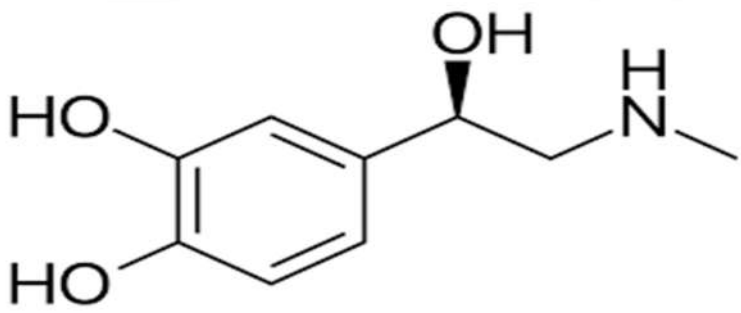
→ Epinephrine is a hormone neurotransmitter. When it is produced in the body, it contracts blood vessels, increases heart rate, dilates air passages, and contributes in the fight-or-flight response of the sympathetic nervous system.

Chemical Name and Structure

1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-,

or

(-)-3,4-Dihydroxy-α-[2(methylamino)ethyl]benzyl alcohol.



Mechanism of Action

➢ Through its action on alpha-1 receptors, epinephrine induces increased vascular smooth muscle contraction, pupillary dilator muscle contraction, and intestinal sphincter muscle contraction.

Uses

- It stimulates the heart, increases heart rate and blood pressure, and relaxes the musculature of intestine and bronchi.
- It is commonly used in acute allergic disorders and histamine reactions.

Stability and Storage Conditions

♦ EpiPen and EpiPen Jr Auto-Injectors and Epinephrine Injection, USP should be stored in the carrier tube provided at a temperature of 20°-25°C (68°-77°F)

Type of Formulation

▪ Injectable solution

Popular Brand Names

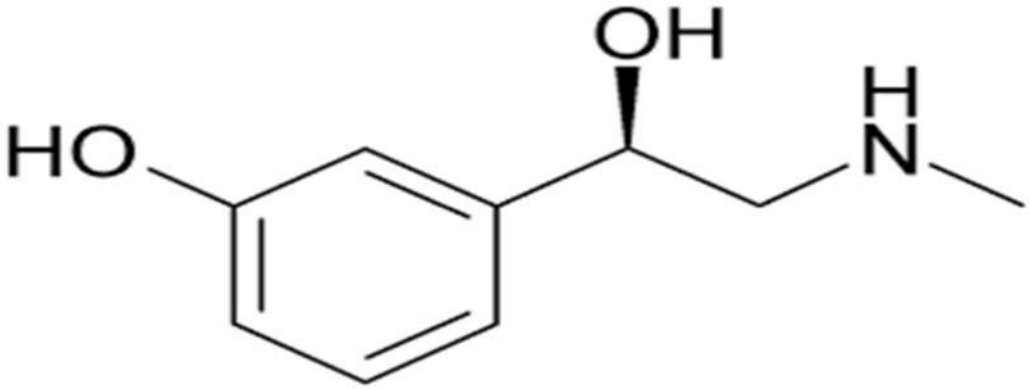
✓ Adrenalin,
✓ Epinephrinesnap-EMS,
✓ EpiPen 2-Pak,
✓ EPlsnap, Auvi-Q, Epinephrinesnap-V, EpiPen JR 2-Pak, Symjepi

Phenylephrine

→ Phenylephrine is sympathomimetic amine acting mostly on the α-adrenergic receptors. It is a vasoconstrictor and used as a nasal decongestant and cardiotonic agent.

Chemical Name and Structure

- (R)-3-[-1-hydroxy-2-(methylamino)ethyl]phenol



Mechanism

➢ Phenylephrine is an agonist of α1-adrenoceptors. Nasal decongestant action is mediated by activation of α1-adrenoceptors in the arterioles of the nasal mucosa. This causes vasoconstriction, which leads to decreased edema and increased drainage of the sinus cavities.

Uses

- Phenylephrine is used to relieve nasal discomfort caused by colds, allergies, and hay fever. It is also used to relieve sinus congestion and pressure. Phenylephrine will relieve symptoms but will not treat the cause of the symptoms or speed recovery.

Stability and Storage Conditions

♦ Protect from light.
♦ It should be store in carton until time of use.

Types of Formulations

▪ Capsules, Solution,
▪ Tablets, Granules

Popular Brand Names

✓ Neo-Synephrine,
✓ Biorphen,
✓ Sudafed PE Congestion,
✓ Suphedrine PE

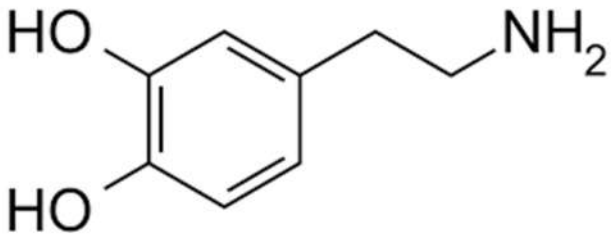
Dopamine *

→ Dopamine (a central neurotransmitter) is a metabolic precursor of nor-epinephrine and epinephrine. It does not Cross the blood brain barrier and thus has minimal effect on the CNS.

→ It acts on the receptors and produces a positive inotropic effect on heart. It increases the systolic and pulse pressures.

Chemical Name and Structure

- 4-(2-aminoethyl) benzene-1,2-diol



Mechanism of Action

➢ Dopamine is administered as a continuous intravenous infusion. At low doses, dopamine preferentially stimulates D1 and D2 receptors in the renal vasculature, which leads to vasodilation and promotes renal blood flow to preserve glomerular filtration.

Uses

- It is used in acute congestive heart failure with imminent renal failure.
- It is used in acute pancreatitis.
- It is used in septic shock and surgical shock.

Stability and Storage Conditions

♦ Dopamine HCI Injection should be stored in such a way that is should avoiding contact with alkalies (including sodium bicarbonate), oxidising agents or iron salts.

Type of Formulation

▪ Injectable solution

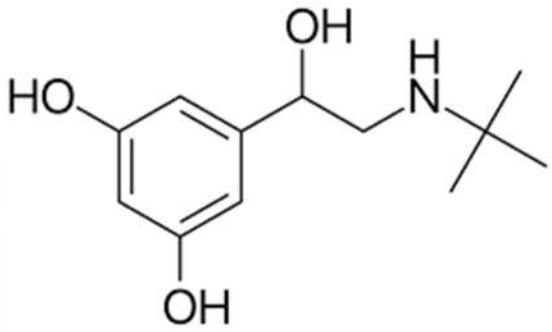
Popular Brand Names

✓ Intropin

Terbutaline

→ Terbutaline is a synthetic compound acting as a sympathomimetic amine. It is the most selective agent which stimulates β2-adrenoreceptors.

Chemical Structure



Mechanism of Action

➢ Terbutaline is a bronchodilator, a medication that dilates (expands) air passages in the lungs. It attaches to beta adrenergic receptors on muscles surrounding the air passages, causing the muscles to relax and dilate the air passages. Wider air passages allow more air to flow in and out of the lungs.

Uses

▪ It is used in breathlessness and wheezing arising from lung problems (e.g., asthma, chronic obstnuctive pulmonary disease, bronchitis, and emphysema).

Stability and Storage Conditions

♦ It should be stored at room temperature and away from light and moisture. It should not be stored in the bathroom.

Types of Formulations

- Powder,
- Solution

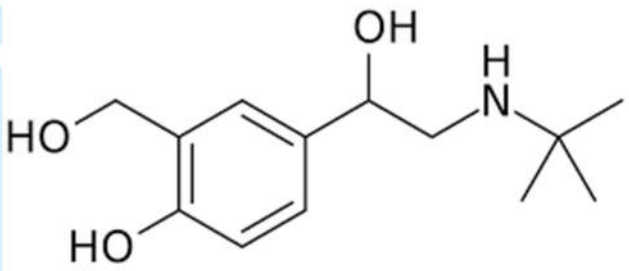
Popular Brand Names

✓ Brethine,
✓ Bricany,
✓ Brethaire

Salbutamol (Albuterol)

→ Salbutamol (INN) is also known as albuterol (USAN). It is as hort-acting β2-adrenergic receptor agonist, employed in the management of bronchospasm seen in asthma and chronic obstructive pulmonary disease.

Chemical Structure



Mechanism of Action

➢ Salbutamol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Salbutamol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges.

Uses

- It is used in bronchial asthma.
- It is used in peripheral vascular diseases.
- It is used in the prevention of premature labour.

Stability and Storage Conditions

- It should be stored at room temperature and keep away from light and moisture.

Types of Formulations

- Aerosol,
- Solution,
- Tablets

Popular Brand Names

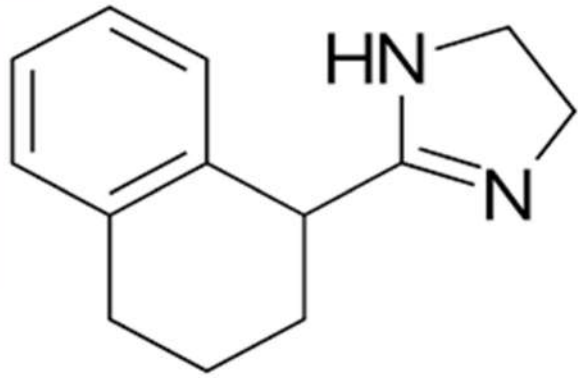
- ✓ Airomir,
- ✓ Proventil,
- ✓ Combivent,
- ✓ Xopenex,
- ✓ Ventolin

Tetrahydrozoline

→ Tetrahydrozoline is an alpha-adrenergic agonist which is used in the treatment of temporary symptomatic relief of discomfort and redness of eyes due to minor irritations, as well as it reduces nasal congestion.

Chemical Name and Structure

- (RS)-2-(1,2,3,4-tetrahydronaphthalen-1-yl)-4,5-dihydro-1H-imidazole



Mechanium of Action

➢ Adrenergic receptors are G-protein-coupled receptors (GPCR) that regulate vascular tone, i.e., vasoconstriction is caused by the stimulation of alpha-1 adrenergic receptors.

Uses

- It acts as a vasoconstrictor by narrowing swollen blood vessels in the eye for reducing eye redness.
- Its ophthalmic preparations (for the eyes) are used for providing temporary relief from minor eve redness, swelling or draining caused by minor irritants.

Stability and Storage Conditions

- It should be stored at room temperature and kept away from moisture and heat.
- The bottle should be tightly closed when it is not in use.

Type of Formulation

♦ Ophthalmic solution

Popular Brand Names

✓ Colirio Ocusan,
✓ Visine.

Indirect Acting Agents

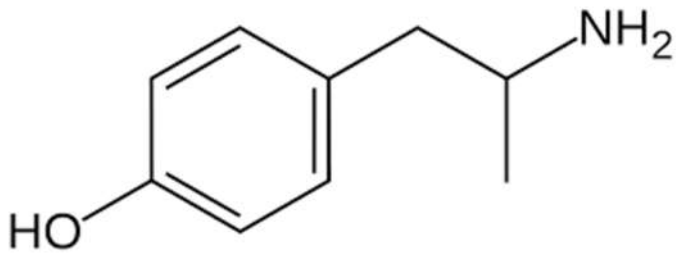
- Indirect acting sympathomimetic agents stimulate the release of a stored neurotransmitter from within the adrenergic nerve terminals. The main neurotransmitter involved here is nor-epinephrine, which on being released stimulates the adrenergic receptors on the effector organs.
- The drugs studied below are:
    1) Hydroxyamphetamine,
    2) Pseudoephedrine.

Hydroxyamphetamine

→ Hydroxyamphetamine occurs as a hydrobromide salt derived from amphetamines. It is a powerful vasoconstrictor which stimulates the α-receptors but lacks any CNS activity.

Chemical Name and Structure

- 4-(2-aminopropyl)phenol



Mechanism of Action

- Hydroxyamphetamine hydrobromide is an indirect acting sympathomimetic agent. It causes mydriasis by releasing nor-epinephrine from adrenergic nerve terminals.

Uses

- It is used in narcolepsy (sudden attack of sleep in completely inappropriate situations
- It is used in children having hyperkinetic syndrome.

Stability and Storage Conditions

- It should be stored between 20°C and 25°C. It should be protected from light and sunlight.

Type of Formulation

- Solution

Popular Brand Name

- ✓ Paremyd

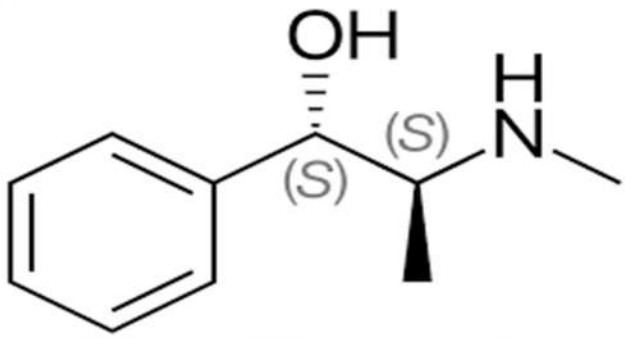
Pseudoephedrine

→ It is a α- and β-adrenergic agonist and a sympathomimetic agent which also increases nor-epinephrine release.

→ It is structurally similar to ephedrine, and relieves nasaid and Sinus congestion. It also relieves otalgia related to air travel, in aduits.

Chemical Name and Structure

- (1R,2R)-2-methylamino-1-phenylpropan-1-ol



Mechanism of Action

➢ Pseudoephedrine is a sympathomimetic with a mixed mechanism of action, direct and indirect. It indirectly stimulates alpha-adrenergic receptors, causing the release of endogenous norepinephrine (NE) from the granularity of neurons, while it directly stimulates beta-adrenergic receptors

Uses

- It is used in vasomotor rhinitis, and nasal, sinus and eustachian tube congestion. It is also used as a first line therapy in priapism.

Stability and Storage Condition

♦ It should be store at room temperature.

Types of Formulations

- Syrup,
- Tablets.

Popular Brand Names

✓ Sudafed Congestion,
✓ SudoGest,
✓ Sudafed 12-Hour,
✓ Sudafed Children's Nasal Decongestant

Agents with Mixed Mechanism

→ Some sympathomimetic agents (e-g ephedrine, metaraminol, and pseudoephedrine) have a mixed action.
→ They act by releasing a neurotransmitter, and also have a direct-agonist activity.
→ Amongst the adrenergic agonists, epinephrine and nor-epinephrine are the least specific.
→ Both α- and β-receptors can be stimulated by nor- epinephrine and epinephrine, but due to the difference in their chemical structures, nor-epinephrine has more pronounced effects at a-receptors while epinephrine has more pronounced effects at β-receptors.Also, the potency of both these drugs is different from each other.

The drugs studied below are:

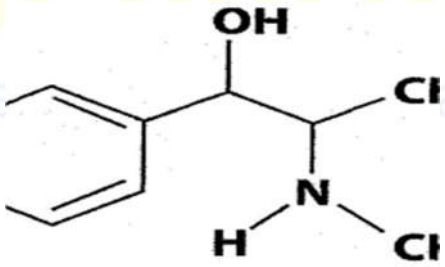
1) Ephedrine,
2) Metaraminol.

Ephedrine

→ Ephedrine acts as an agonist On α-receptor as well as on β-receptor. It also increases the release of nor-epinephrine from the sympathetic neurons Thus, it is a mixed-acting sympathomimetic drug The Structure of ephedrine involves two asymmetrical arbon atoms. The clinically used forms of ephedrine 1 - ephedrine and racemic ephedrine only.

Chemical Name and Structure

- rel-(R,S)-2-(methylamino)-1-phenylpropan-1-ol



ephedrine

Mechanism of Action

➢ Ephedrine, a sympathomimetic amine, acts on part of the sympathetic nervous system (SNS). The principal mechanism of action relies on its **indirect stimulation of the adrenergic receptor system by increasing the activity of norepinephrine at the postsynaptic α and β receptors**.

Uses

- Ephedrine and its salts are used in allergic disorders, colds, narcolepsy through oral, intravenous, intramuscular, and topical route, hypotensive conditions,

Stability and Storage Conditions

♦ This medication should be stored at room temperature.

Types of Formulations

- Tablets,
- Capsules

Popular Brand Names

- ✓ Akovaz,
- ✓ Bronkaid,
- ✓ Corphedra,
- ✓ Primatene, Rezipres, Emerphed

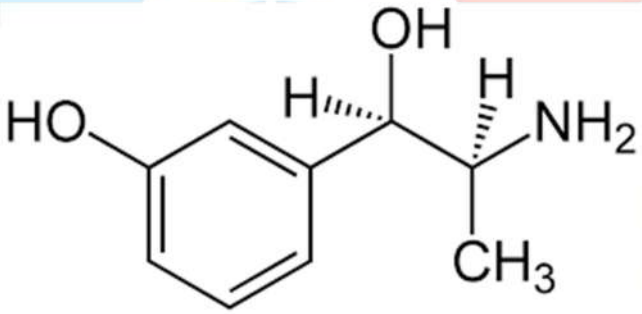
Metaraminol

→ Metaraminol (or aramine) is structurally similar to phenylephrine with the only difference that it is a primary (and not secondary) amine.

→ It directly acts on a-adrenergic receptors and has mixed mechanism of action.

Chemical Name and Structure

- (1R,2S)-3-[-2-amino-1-hydroxy-propyl]phenol



Mechanism of Action

➢ Metaraminol acts through peripheral vasoconstriction by acting as a pure alpha-1 adrenergic receptor agonist, consequently increasing systemic blood pressure (both systolic & diastolic). Its effect is thought to be associated with the inhibition of adenyl cyclase which leads to an inhibition of the production of cAMP.

Uses

- Parenterally it is used as a vasopressor for treating and preventing acute hypotensive state arising due to spinal anaesthesia.

Stability and Storage Conditions

- It should be stored between 20°C and 25°C. It should be protected from light and sunlight.

Type of Formulation

- ♦ Solution

Popular Brand Name

- ✓ Aramine

ADRENERGIC ANTAGONISTS (SYMPATHOLYTIC AGENTS)

→ Adrenoceptor antagonists or adrenergic blocking agents or anti-adrenergic drugs block the responses mediated by adrenoceptor activation. In other words, they inhibit the actions that occur by the release of adrenaline.

→ The action of sympathomimetic amines is selectively blocked by the anti-adrenergic drugs by acting either on the α- or β-receptors or on both of them. It brings about opposite effects of the catecholamines facilitated through the α-or β- receptors.

→ Based on receptor selectivity, the α-and β-adrenoceptor blocking agents are divided into primary sub-groups.

→ All of these agents have pharmacological antagonist or partial agonist property.

→ A majority of them act competitively and have reversible actions.

Classification

- α-Adrenoceptpor Blocking Drugs :
- β-Adrenoceptpor Blocking Drugs :

α-Adrenoceptpor Blocking Drugs : The effect of catecholamines facilitated via α-receptors are blocked by these agents furthermore, depending on the ability of these drugs to dissociate from the receptors, they may either be reversible or irreversible.

The drugs studied below are :

1. Tolazoline,
2. Phentolamine,
3. Phenoxybenzamine,
4. Prazosin.

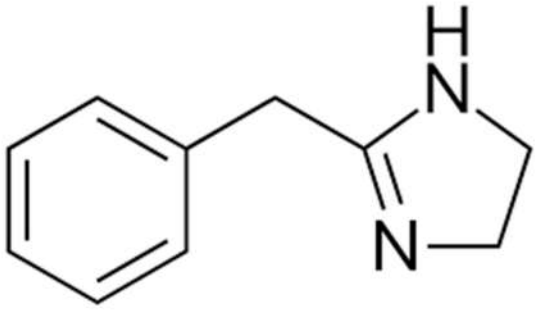
Tolazoline

→ Tolazoline (an imidazoline derivative) is a competitive α-adrenergic antagonist.

→ It possesses like affinity for both α1- and α2-receptors.

Chemical Name and Structure

- 2-Benzyl-4,5-dihydro-1H-imidazole



Mechanism of Action

- An alpha-adrenergic blocking agent, tolazoline HCl is structurally related to phentolamine. By directly relaxing vascular smooth muscle, tolazoline has peripheral vasodilating effects and decreases total peripheral resistance. Tolazoline also is a competitive alpha1 and alpha2 adrenergic blocking agent.

Uses

- ♦ It is used as a vasodilator and for stimulating heart and causing mydriasis through its sympathomimetic effect)

Stability and Storage Conditions

- ▪ It should be stored at room temperature.

Type of Formulation

- • Injection solution

Popular Brand Name

- ✓ Priscoline Hydrochloride

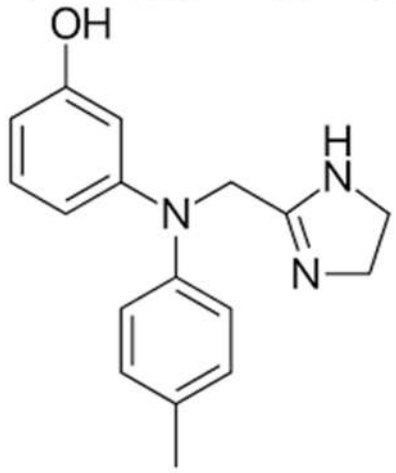
Phentolamine

→ The group attached to the imidazoline ring decides whether it will be an agonist or an antagonist.

→ Two imidazoline α-antagonists used therapeutically are tolazine (Priscoline) and phentolamine (Regitine). Both of them are competitive (reversible) blocking agents.

Chemical Name and Structure

- ▪ 3-[(4,5-Dihydro-1H-imidazol-2-ylmethyl)(4-methylphenyl)amino]phenol



Mechanism of Action

- ➢ Phentolamine produces its therapeutic actions by competitively blocking alpha-adrenergic receptors (primarily excitatory responses of smooth muscle and exocrine glands), leading to a muscle relaxation and a widening of the blood vessels. This widening of the blood vessels results in a lowering of blood pressure.

Uses

- • Phentolamine is used for diagnosing pheochromocytoma (tumours of adrenal medulla).

Stability and Storage Conditions

- ▪ Phentolamine mesylate injection is stable for 48 hours at room temperature or 1 week at 2°-8 °C.

Types of Formulations

- ♦ Powder for injection,
- ♦ Injection Solution

Popular Brand Names

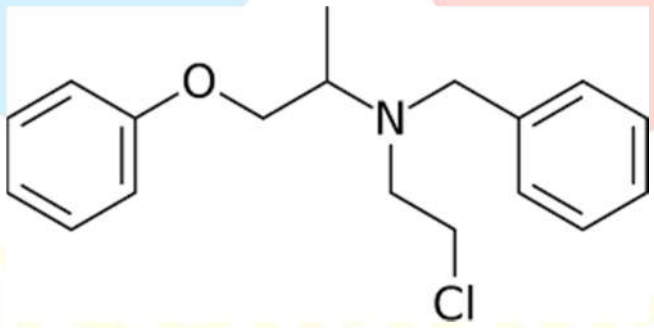
- ✓ Oraverse,
- ✓ Rogitine

Phenoxybenzamine

→ Phenoxybenzamine is α-adrenergic antagonist with long duration of action. It is used as an anti-hypertensive and as a peripheral vasodilator.

Chemical Name and Structure

- (RS)-N-Benzyl-N-(2-chloroethyl)-1-phenoxypropan-2-amine



Mechanism of Action

- ➢ Phenoxybenzamine widens blood vessels and relaxes muscles by blocking α-receptors. Blood pressure reduces due to widened blood vessels.

Uses

- ▪ It is used for treating pheochromocytoma and Raynaud's syndrome.

Stability and Storage Conditions

- ♦ It should be stored at 25°C (77°F)

Type of Formulation

- Capsules

Popular Brand Name

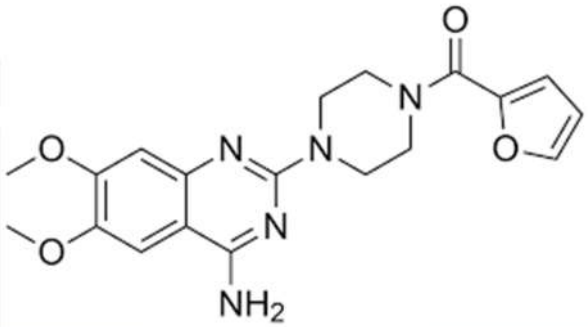
- ✓ Dibenzyline

Prazosin

→ Prazosin is derived from quinazoline and is a highly specific antagonist of α1-receptor) Structurally, it has a quinazoline ring, a piperazine ring).

Chemical Name and Structure

- [4-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-1-piperazinyl](2-furyl)methanone



Mechanism of Action

➢ Prazosin **inhibits the postsynaptic alpha-1 adrenoceptors**. This inhibition blocks the vasoconstricting (narrowing) effect of catecholamines (epinephrine and norepinephrine) on the vessels, leading to peripheral blood vessel dilation.

Uses

- It is used in hypertension, symptomatic benign prostatic hyperplasia, and severe congestive heart failure.

Stability and Storage Conditions

♦ It should not be stored in the bathroom. Keep all medicines away from children.

Type of Formulation

▪ Capsules

Popular Brand Names

✓ Minipress,
✓ Prazin,
✓ Prazo

β-Adrenoceptpor Blocking Drugs : The effect of catecholamines facilitated via β-adrenoceptors are blocked by β- adrenoceptor blocking drugs. They can further be categorised as selective or non-selective β- adrenoceptor blocking drugs.

The drugs studied below are:

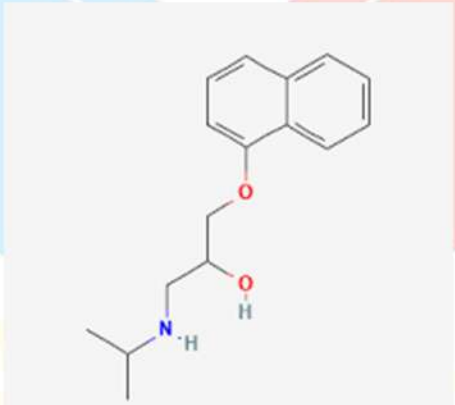
1. Propranolol, *
2. Ateolol, *
3. Carvedilol.

Propranolol *

→ Propranonol is a sympatholytic non-selective first successful β-blocker. Sympatholytics treat hypertension, anxiety, and panic.

Chemical Name and Structure

- 1-naphthalen-1-yloxy-3-(propan-2-ylamino)propan-2-ol;hydrochloride



Mechanism of Action

➢ Propranolol is a non-selective beta receptor antagonist. This means that it does not have preference to Beta-1 or Beta-2 receptors. It competes with sympathomimetic neurotransmitters for binding to receptors, which inhibits sympathetic stimulation of the heart.

Uses

▪ Tremors, angina (chest pain), hypertension (high blood pressure), heart rhythm disorders, and other heart or Circulatory conditions can be treated using propranolol

Stability and Storage Conditios

- Tablets and capsules should at a room temperature with tightly closed container

Types of Formulations

♦ Solution,
♦ Tablets

Popular Brand Name

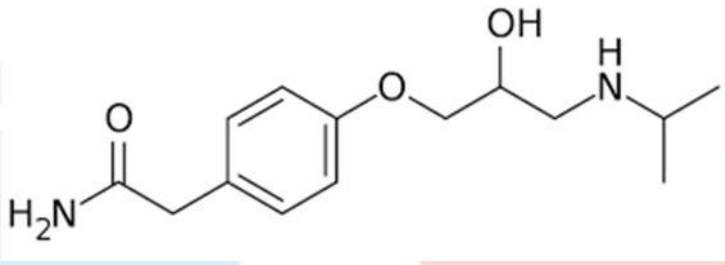
✓ Hemangeol,
✓ Hemangiol,
✓ Inderal,
✓ Innopran

Atenolol *

→ Atenolol is a cardioselective β-adrenergic blocker having potency and properties similar to propranolol, excluding the negative inotropic effect.

Chemical Name and Structure

- 2-[4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl]acetamide



Mechanism of Action

➢ Atenolol belongs to a class of drugs known as beta blockers. It works by blocking the action of certain natural chemicals in your body, such as epinephrine, on the heart and blood vessels. This effect lowers the heart rate, blood pressure, and strain on the heart.

Uses

♦ It is used in angina pectoris and hypertension for long-term treatment.

Stability and Storage Conditions

▪ It should be stored at room temperature between 68°F and 77°F (20°C and 25°C).

Type of Formulation

- Tablets

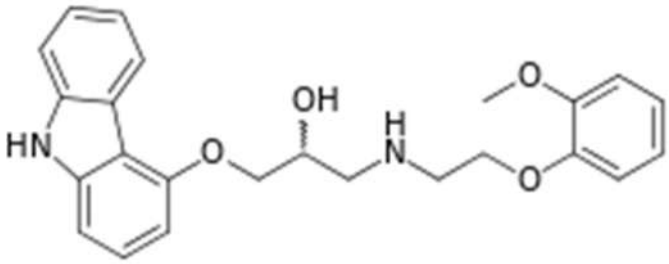
Popular Brand Name

✓ Tenormin

Carvedilol

→ Carvedilol is a non-selective β-blocker prescribed for treating mild to moderate congestive heart failure. It blocks β_1- ,β_2-, and α-adrenergic receptors.

Chemical Structure



Mechanism of Action

- Carvedilol works by blocking the action of certain natural substances in your body, such as epinephrine, on the heart and blood vessels. This effect lowers your heart rate, blood pressure, and strain on your heart. Carvedilol belongs to a class of drugs known as alpha and beta-blockers.

Uses

- It is used for treating mild to moderate heart failure of cardiomyopathic or ischemic origin

Stability and Storage Conditions

- Carvedilol tablet should be stored at 20° to 25°C (68° to 77'F). The tablets should be kept dried. The expired tablet should be safely discarded.

Type of Formulation

- Tablets

Popular Brand Name

- Coreg

CHOLINERGIC DRUGS AND RELATED AGENTS (PARASYMPATHOMIMETRIC)

→ The following two ways increase the stimulation of Acetylcholine Receptors (AChR):

→ **Binding the direct acting cholinergic agonists** to the AChR, thereby, triggering nicotinic or muscarinic effects, or both, and

→ **Binding the indirect acting cholinergic agonists** to the AChR that inhibit the hydrolysis of ACh by AChE, thereby, extending the action of available ACh.

- The hydrochloride salt of cholinergic agonist exists in the form of white crystalline powder or colourless crystals.
- It has a faint bitter taste and does not have any odour.
- It is hygroscopic and shows high solubility in water.
- Since these agents are affected by light, they are stored in tightly- closed, light-resistant containers.
- lts solutions maintained at a pH between 4 and 5 are the most stable. In the presence of Strong acids and alkalis. its solutions degrade and undergo epimerisation.

Classification

- Direct Acting Agents (Cholinergic Agonists)
- Indirect Acting Agents (Anticholinesterase)

Direct Acting Agents

→ The structure and effect of cholinergic agonists is similar to that of ACh.

→ Cholinergic agonists directly bind The bind to and activate the ACh receptors (either muscarinic or nicotinic receptors).

→ Cholinergic agents include methacholine, carbachol. bethanechol, and and pilocarpine.

The drugs studied below are

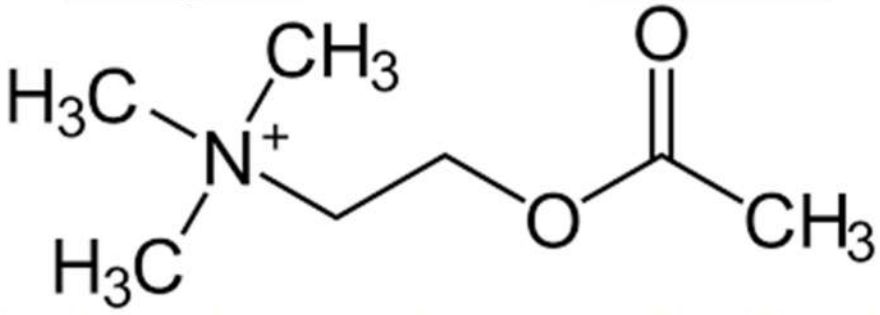
- Acetylcholine, *
- Carbachol,
- Pilocarpine.

Acetylcholine *

→ Acetylcholine is a neurotransmitter. In vertebrates, it is the major transmitter at neuromuscular junctions, parasympathetic effector junctions, autonomic ganglia, many sites in the CNS, and a subset of sympathetic effector junctions.

Chemical Name and Structure

- 2-Acetoxy-N,N,N-trimethylethanaminium



Mechanism of Action

➢ The mechanism of action of acetylcholine is as a Cholinergic Agonist. A neurotransmitter. Acetylcholine in vertebrates is the major transmitter at neuromuscular junctions, autonomic ganglia, parasympathetic effector junctions, a subset of sympathetic effector junctions, and at many sites in the central nervous system.

Uses

▪ It is used in cataract surgery, keratoplasty, iridectomy for obtaining meiosis of the iris in seconds after delivery of lens and in other anterior segment surgeries in which rapid meiosis may be required.

Stability and Storage Conditions

- It should be stored at room temperature. Away from light.

Types of Formulations

♦ Powder for injection,

♦ Gels,

♦ Lozenges

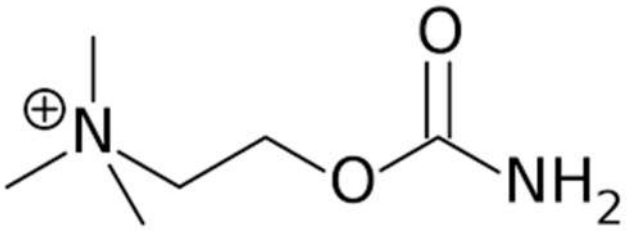
Popular Brand Name

▪ Miochol-E

Carbachol

→ Carbachol is chemically a carbamate, thus, possesses a very high potency (as opposed to esters). Another added advantage with this drug is that it undergoes slow hydrolysis. It decreases the intraocular pressure and is therefore employed in glaucoma treatment.

Chemical Structure



Mechanism of Action

➢ Mechanism : Carbachol is a potent cholinergic (parasympathomimetic) agent which produces constriction of the iris and ciliary body resulting in reduction in intraocular pressure. The exact mechanism by which carbachol lowers intraocular pressure is not precisely known.

Uses

- It is used for treating intestinal and bladder atony seen post-operatively.

Stability and Storage Conditions

- It should be stored under dry conditions.
- The product can be stored for upto 12 months.

Types of Formulations

- Tablet,
- Solution

Popular Brand Names

✓ Carbastat,
✓ Miostat

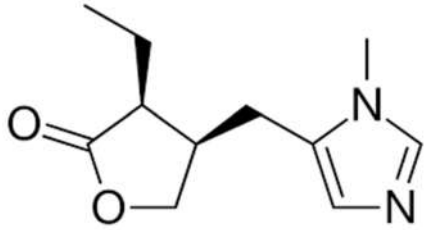
Pilocarpine

→ Pilocarpine is a parasympathomimetic alkaloid derived from the leaves of tropical American shrubs of Pilocarpus genus.

→ When applied topically in conditions of glaucoma and xerostomia, it acts therapeutically at muscarinic acetylcholine receptor M3 as it is a non-selective muscarinic receptor agonist in the parasympathetic nervous system.

Chemical Name and Structure

- (3S,4R)-3-Ethyl-4-((1-methyl-1H-imidazol-5-yl)methyl)dihydrofuran-2(3H)-one



Mechanism of Action

➢ Pilocarpine is a cholinergic parasympathomimetic agent which acts by stimulating the muscarinic receptors; thus, increases the secretions by exocrine glands, produces contraction of the iris sphincter muscle and ciliary muscle (when applied topically to the eyes).

Uses

- Pilocarpine is used for treating xerostomia occurring after head and neck radiation treatments, or in Sjorgen's syndrome (an autoimmune disorder mainly affecting females).

Stability and Storage Conditions

- All medicines should be kept out of reach and sight of children.
- It should be stored in cool, dry place and also kept away from direct heat and light.

Types of Formulations

- Tablets,
- Solution

Popular Brand Name

✓ Salagen

Cholinesterase Inhibitors (Indirect Acting Agents)

→ Acetylcholine neurotransmitter is inactivated by the enzyme cholinesterase which is inhibited by the indirect acting cholinergic agents or anticholinesterases.

→ Thus, the inactivation of ACh is prevented as a result of which the level of endogenous ACh at the neuroeffector junction of paras arasympathetic nerve endings or the neuromuscular junction increase.

→ This accumulated ACh are made available for attachment to the receptor site in order to produce cholinergic responses.

→ But in case of blockage of ACh receptors, this increased level of ACh competes with the blocking drug for the receptors, and thus reverses the blockage.

→ This results in the resumption of nerve transmission either at the parasympathetic terminal site or at the neuromuscular junction.

The drugs studied below are:

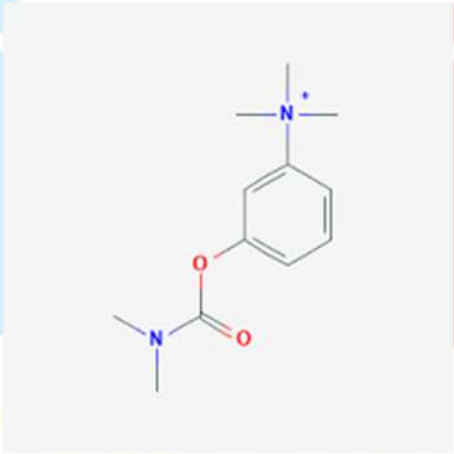
- Neostigmine, *
- Edrophonium chloride,
- Tacrine hydrochloride,
- Echothiophate iodide.

Neostigmine *

→ Neostigmine is a parasympathomimetic acting as a reversible acetylcholinesterase inhibitor.

Chemical Name and Structure

- 3-(dimethylcarbamoyloxy)phenyl]-trimethylazanium



Mechanism of Action

➢ At the neuromuscular junction neostigmine produces the concentrationof skeletal muscle by two ways:

1. By acting directly on the skeletal muscle, and
2. By inactivating the cholinesterase enzyme (as in physostigmine).

Uses

- It is used for urinary retention caused by general anaesthesia and to treat curariform drug toxicity.
- It is also used in the Ogilvie syndrome (pseudo- obstruction of colon in critically ill patients),
- It has been used as a test for early pregnancy.

Stability and Storage Conditions

- lt should be protected from light and should be stored at temperature less than 25°C.
- It should be stored in carton- until the time of use.

Type of Formulation

♦ Injectable solutions

Popular Brand Names

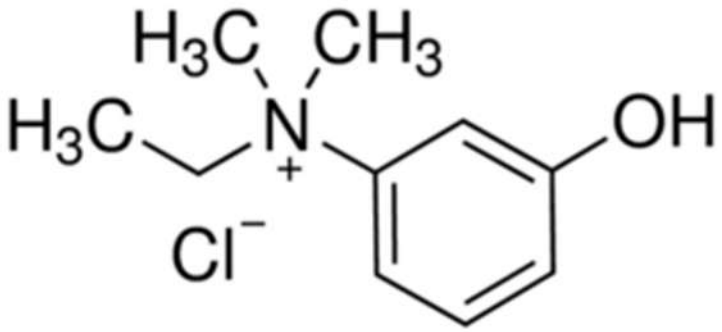
✓ Bloxiverz,
✓ Prostigmin Bromide,
✓ Prostigmin

Edrophonium Chloride

→ Edrophonium chloride is a short and rapid-acting anticholinesterase drug.

Chemical Name and Structure

- ethyl-(3-hydroxyphenyl)dimethylammonium chloride



Mechanism of Action

➢ Edrophonium chloride inhibits the acetylcholinesterase enzyme, and subsequently increases the duration of action of ACh, occurring naturally in the body. Acetylcholine stimulates nicotinic and muscarinic receptors having various effects.

Uses

▪ It is used as an adjunct for differential diagnosis of myasthenia gravis, and also for determining the treatment requirements.

Stability and Storage Conditions

♦ It should be stored at controlled room temperature 15° 30°C (59°-86°F).

Type of Formulation

- Injectable solutions

Popular Brand Names

✓ Enlon,
✓ Reversol,
✓ Tensilon

Tacrine Hydrochloride

→ Tacrine hydrochloride is a reversible cholinesterase inhibitor and a parasympathomimetic agent which is prescribed for treating mild to moderate dementia of Alzheimer's type.

Chemical Structure



Mechanism of Action

- ➢ Although the mechanism of action has not been fully elucidated, tacrine hydrochloride may bind reversibly to cholinesterase, acetylcholinesterase as well as butyrylcholinesterase, thereby decreasing the breakdown of acetylcholine, and prolonging synaptic actions as well as increased release of acetylcholine.

Uses

- ✓ It is used as a respiratory stimulant, for countering the effect of muscle relaxants, and for treating Alzheimer's disease and other CNS disorders.

Stability and Storage Conditions

- ▪ Capsules should be stored at room temperature, 15°-30° C (59°-86° F).

Type of Formulation

- ♦ Capsules

Popular Brand Name

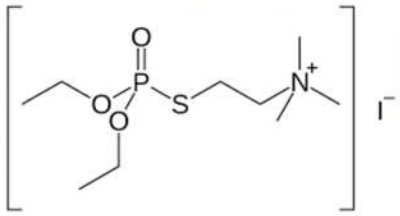
- ✓ Cognex

Echothiophate iodide

→ Echothiophate iodide is a long-acting, irreversible, potent cholinesterase inhibitor used as an ocular hypertensive for treating glaucoma.

Chemical Name and Structure

- 2-(Diethoxyphosphorylsulfanyl)ethyl-N,N,N-trimethylazanium iodide



Mechanism of Action

- ➢ Echothiophate is an indirect-acting parasympathomimetic agent. By interfering with the enzymatic destruction of acetylcholine, echothiophate potentiates the action of acetylcholine at cholinergic synapses. The pupil of the eye is constricted by contraction of the iris sphincter, producing miosis.

Uses

- → It is used for treating sub-acute or chronic angle-closure glaucoma after iridectomy or when surgery is denied or contraindicated.

Stability and Storage Conditions

- It should be stored under refrigeration between 2-8°C.

Types of Formulations

- ▪ Solution,
- ▪ Powder

Popular Brand Name

- ✓ Phospholine Iodide

Cholinesterase Reactivator – Pralidoxime Chloride

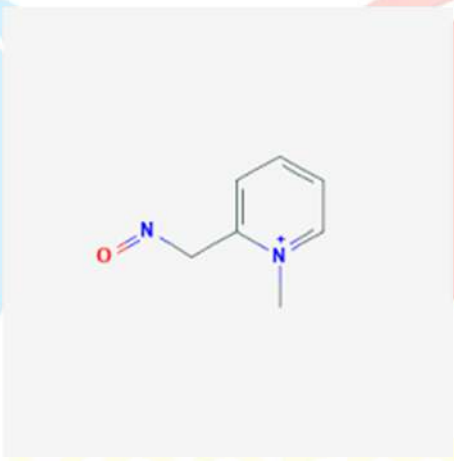
→ Cholinesterase reactivators are used for reversing the inactivation of cholinesterase by organophosphates or sulphonates.

→ They are used as a therapy in agricultural, by industrial, and military poisonings caused organophosphates and sulfonates.

→ Pralidoxime chloride is used as by an antidote in poisoning caused organophosphate pesticides and chemicals.

Chemical Name and Structure

- 2-formyl-1-methylpyridinium chloride oxime.



Mechanism of Action

➢ The principal action of pralidoxime is to reactivate cholinesterase (mainly outside of the central nervous system) which has been inactivated by phosphorylation due to an organophosphate pesticide or related compound.

Uses

- It is used for treating the poisoning caused by pesticides and chemicals organophosphates having of anticholinesterase activity.
- It is also used for controlling the overdosage of anticholinesterase drugs used for treating myasthenia gravis.

Stability and Storage Conditions

- It should be stored at 20°-25°C (68°-77°F).

Type of Formulation

♦ Injection

Popular Brand Names

✓ Atnaa,
✓ Duodote,
✓ Protopam

CHOLINERGIC BLOCKING AGENTS (CHOLINERGIC ANTAGONISTS)

→ Anticholinergic or parasympatholytic drugs are those drugs which occupy the ACh receptors (and do not allow ACh to bind to the receptors) and prevent the actions of ACh.
→ Parasympatholytic drugs are also termed as cholinergic blocking agents, cholinergic or muscarinic antagonists, anti-parasympathetic agents, anti-muscarinic agents, and antispasmodics.
→ The heart, respiratory tract, GI tract, urinary bladder, eyes, and exocrine glands are the major tissues affected by anticholinergic drugs.

Classification

Anti-Muscarinic Agents/Muscarinic Antagonists:

- These compounds exhibit high binding affinity for muscarinic receptors.
- They do not have any intrinsic activity.
- According to the proposed mechanism, binding in of an antagonist to the receptor results in a conformational change in the receptor protein.
- This change is different from that produced when an agonist binds to the receptor.
- Thus, binding of an antagonist to the receptor does not produce any response. of Examples anti-muscarinicsare atropine, scopolamine, tolterodine, homatropine, tropicamide, etc.

Anti-NicotinicAgents/NicotinicAntagonists: These chemical compounds bind to the cholinergic nicotinic receptors These agents, however, are not efficacious.

The drugs studied below are:

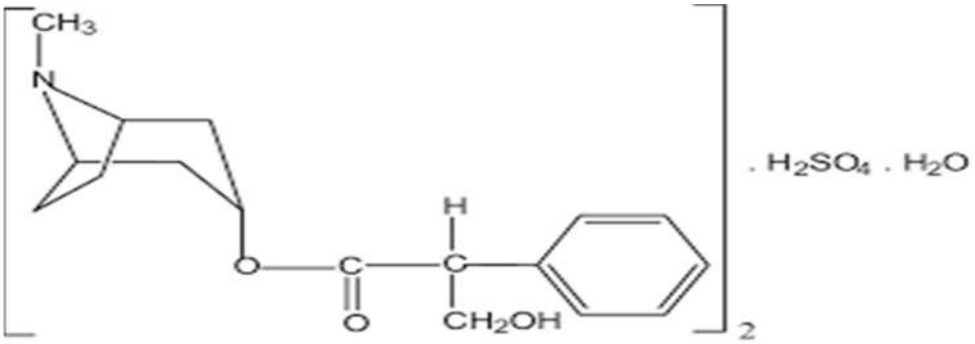
- Atropine sulphate, *
- Ipratropium bromide.

Atropine Sulphate *

→ Atropine sulphate is an alkaloid derived from Atropa belladonna and some other plants also of Solanaceae family.

Chemical Name and Structure

- (1R,3R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl hydroxy-2-phenylpropanoate



Mechanism of Action

- Atropine produces a wide range of anticholinergic effects by binding to and inhibiting the muscarinic acetylcholine receptors.

Uses

- It is used for treating poisoning caused by organophosphorous nerve agents with anti-cholinesterase activity (cholinesterase inhibitors) and organophosphorous or carbamate insecticides.

Stability and Storage Conditions

- It should be stored in single or multiple-dose containers, preferably glass, at a temperature of less than 40°C (preferably between 15°-30°C). It should be protected from light and stored in airtight containers.

Type of Formulation

- Injection Solution

Popular Brand Names

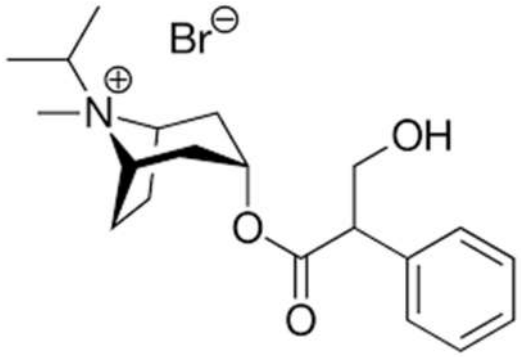
- ✓ Atnaa,
- ✓ Busulfex,
- ✓ Donnatal,
- ✓ Duodote, etc,

Ipratropium Bromide

→ Ipratropium is a muscarinic antagonist having similar structure to atropine but is considered safer and more effective for inhalational uses.

Chemical Name and Structure

- [8-methyl-8-(1-methylethyl)- 8-azoniabicyclo[3.2.1] oct-3-yl] 3-hydroxy-2-phenyl-propanoate



Mechanism of Action

- Ipratropium is an acetylcholine antagonist via blockade of muscarinic cholinergic receptors. Blocking cholinergic receptors decreases the production of cyclic guanosine monophosphate (cGMP). This decrease in the lung airways will lead to decreased contraction of the smooth muscles.

Uses

- ♦ It is used for maintenance and treatment of bronchospasm related to chronic obstructive pulmonary diseases such as chronic bronchitis and emphysema.

Stability and Storage Conditions

- It should not be stored above 25°C. It should be stored in the original package. Before using, the ampoule should be opened immediately and any solution remaining after use should be discarded.

Types of Formulations

- ▪ Spray,
- ▪ Solution

Popular Brand Names

- ✓ Atrovent,
- ✓ Ipratropium Inhalation Solution,
- ✓ Ipratropium Inhalation Aerosol

Synthetic Cholinergic Blocking Agents

→ The solanaceous alkaloids are potent parasympatholytics, but they produce a wide range of undesired effects through their non-specific blockade of autonomic functions.
→ When alkaloids are used for their antispasmodic effects they often give rise to side effects like dryness of the mouth and fluctuations in pulse rate.
→ Hence, synthesis of Compounds having specific cholinolytic actions is desirable.
→ Synthetic cholinergic blocking agents are aminoalcohols in the form of ester, ether, or alcohol.
→ These agents help to produce the effect by blocking the muscarinic action.
→ They are less potent when compared to solanaceous alkaloids.
→ Some examples are tropicamide, dicyclomine hydrochloride, and procyclidine hydrochloride.

The drugs studied below are:

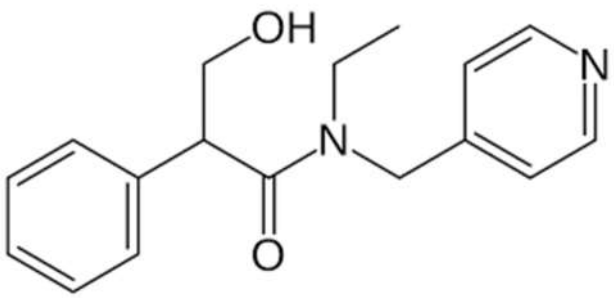
- Tropicamide,
- Cyclopentolate hydrochloride,
- Clidinium bromide, and
- Dicyclomine hydrochloride. *

Tropicamide

→ Tropicamide is a muscarinic antagonist having pnarmacological actions similar to atropine and is mainly used as an ophthalmic parasympatholytic or mydriatic.

Chemical Name and Structure

- Benzeneacetamide, N-ethyl-α-(hydroxymethyl)-N-(4-pyridinylmethyl)-.



Mechanism of Action

- ➢ Tropicamide binds with the receptors in the eye muscles (M receptors) and blocks them. It dilates the pupil and paralyses ciliary muscle by blocking the responses of iris sphincter muscle to the iris and of ciliary muscles to cholinergic stimulation.

Uses

- It is prescibed for inducing mydriasis (pupil dilation) and cycloplegia (paralysis of the ciliarymuscle of the eye) during diagnostic procedures like measurement of refractive errors and for examining the fundus of the eye.

Stability and Storage Conditions

- ✓ It should be stored at 20° to 25°C. The container should be tightly closed.

Types of Formulations

- ♦ Injection,
- ♦ Solution

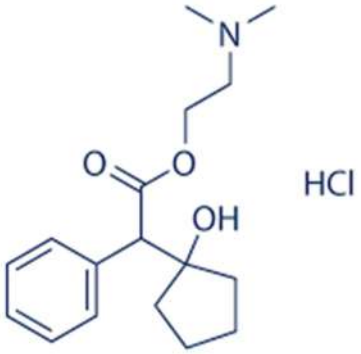
Popular Brand Names

- ✓ Minims Tropicamide,
- ✓ Mydriacyl,
- ✓ Paremyd

Cyclopentolate Hydrochloride

→ Cyclopentolate hydrochloride is a parasympatholytic anticholinergic used only for obtaining mydriasis or cycloplegia.

Chemical Structure



Mechanism of Action

- ➢ It causes mydriasis, i.e., dilates the pupil, and prevents the eye from accommodating for near vision (cycloplegia) by blocking the muscarinic receptors.

Uses

- It is used for producing mydriasis and cycloplegia during diagnostic procedures.

Stability and Storage Conditions

- ✓ A refrigerator should be used for storing some brands of cyclopentolate eye drops.

Type of Formulation

- ♦ Solution

Popular Brand Names

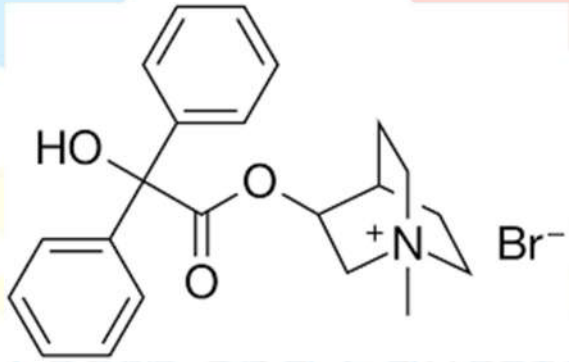
- ✓ Cyclogyl,
- ✓ AK-Pentolate

Clidinium Bromide

→ Clidinium bromide is a synthetic anticholinergic agent having a pronounced antispasmodic and anti-secretory effects on the gastrointestinal tract.

Chemical Name and Structure

- 3-[(2-hydroxy-2,2-diphenylacetyl)oxy]-1-methyl-1-azabicyclo[2.2.2]octan-1-ium bromide



Mechanism of Action

- ➢ Clidinium is a synthetic anticholinergic agent which has been shown in experimental and clinical studies to have a pronounced antispasmodic and antisecretory effect on the gastrointestinal tract. It inhibits muscarinic actions of acetylcholine at postganglionic parasympathetic neuroeffector sites.

Uses

- It is used for treating peptic ulcer diseases.

Stability and Storage Conditions

- ✓ It should be stored at a temperature of -20°C for 2 years or less than 2 years.

Types of Formulations

- ♦ Tablet,
- ♦ Capsules

Popular Brand Name

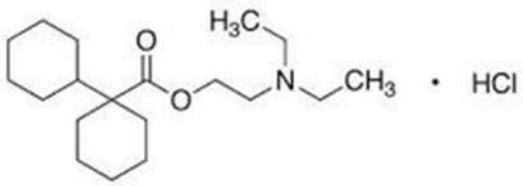
- ✓ Quarzan

Dicyclomine Hydrochloride *

→ Dicyclomine hydrochloride is a bicyclohexyl)-1-carboxylic acid 2-(diethylamino) ethyl ester hydrochloride

Chemical Name and Structure

- 2-(Diethylamino)ethyl 1-cyclohexylcyclohexane-1- carboxylate



Mechanism of Action

- **Dicyclomine hydrochloride acts by the following two mechanisms:**
  - By exerting an anticholinergic effect (anti-muscarinic. specifically) at receptor sites of ACh, and
  - By affecting the smooth muscles directly (musculotropic action).

Uses

- Dicyclomine is employed in the treatment of irritable bowel syndrome, since it decreases the symptoms of stomach and intestinal cramping. It slows down the gut movement and relaxes the muscles of stomach and intestines.

Stability and Storage Conditions

- The container should be tightly closed and should be stored in a dry, cool and well-ventilated place,

Types of Formulations

- Capsule,
- Solution,
- Syrup,
- Tablet

Popular Brand Names

- ✓ Berntyl,
- ✓ Dibent,
- ✓ Dicyclocot