BP402T. MEDICINAL CHEMISTRY – I (Theory)
UNIT – TWO

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UNIT- II **10 Hours**

Drugs acting on Autonomic Nervous System

Adrenergic Neurotransmitters:

Biosynthesis and catabolism of catecholamine.

Adrenergic receptors (Alpha & Beta) and their distribution.

Sympathomimetic agents: SAR of Sympathomimetic agents

Direct acting: Nor-epinephrine, Epinephrine, Phenylephrine*, Dopamine, Methyldopa, Clonidine, Dobutamine, Isoproterenol, Terbutaline,

Salbutamol*, Bitolterol, Naphazoline, Oxymetazoline and Xylometazoline.

- Indirect acting agents: Hydroxyamphetamine, Pseudoephedrine, Propylhexedrine.
- Agents with mixed mechanism: Ephedrine, Metaraminol.

Adrenergic Antagonists:

Alpha adrenergic blockers: Tolazoline*, Phentolamine, Phenoxybenzamine, Prazosin, Dihydroergotamine, Methysergide.

Beta adrenergic blockers: SAR of beta blockers, Propranolol*, Metibranolol, Atenolol, Betazolol, Bisoprolol, Esmolol, Metoprolol, Labetolol, Carvedilol.

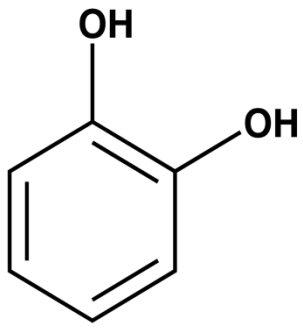
DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM

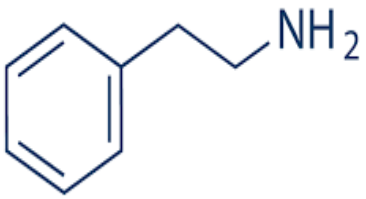
Adrenergic drug exert their principle pharmacological and therapeutic effects either by enhancing or reducing the activity of the various components of the sympathetic division of autonomous nervous system. In general substances that produce effects similar to stimulation sympathetic nervous system are known as sympathomimetic or adrenergic stimulants. Those that decrease sympatholytic activity are referred to sympatholytic adrenergic blocking agents.

Adrenergic agents act on receptors or affect the life cycle of adrenergic neurotransmitters (NTS), including norepinephrine (NE, noradrenaline), Epinephrine (E adrenaline) & Dopamine (DA). These neurotransmitters modulate many vital functions such as rate k force of cardiac contraction, constriction & dilation of blood vessels & bronchioles, the release of the insulin & the breakdown of fat therefore adrenergic drug constitute a broad class of agents

ADRENERGIC NEUROTRANSMITTERS

Norepinephrine, Epinephrine, Dopamine are chemically catecholamine (CAs) which refers generally all organic compounds that contain a catechol nucleus (ortho-dihydroxybenzene) & an ethylamine group.





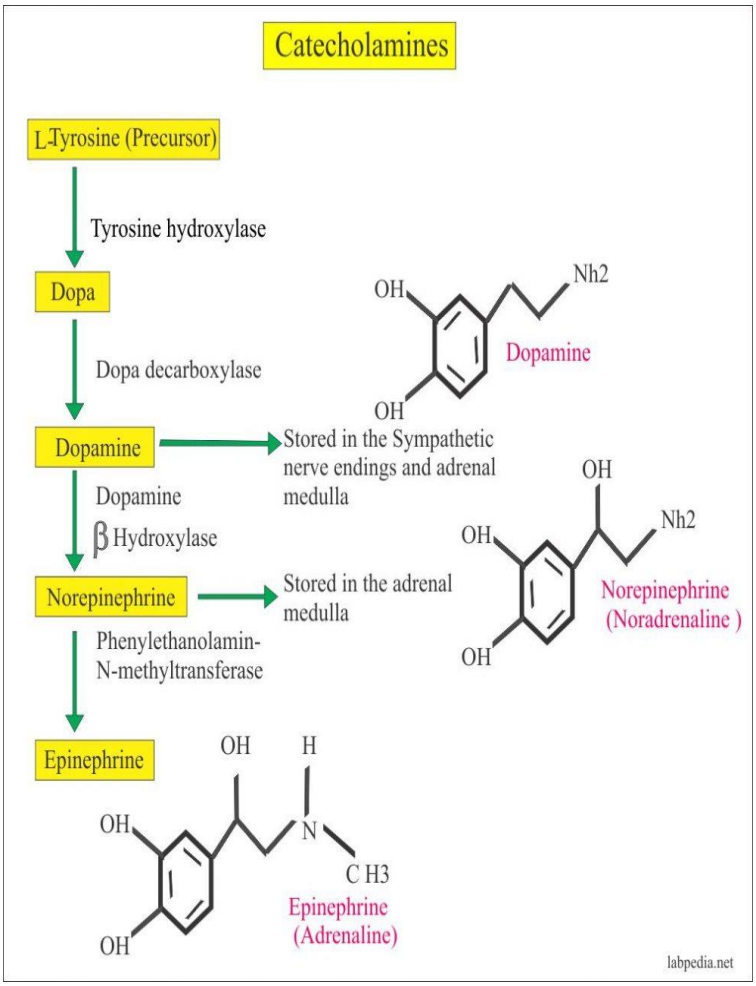
Catechol **Beta-phenylethylamine**

BIOSYNTHESIS

The catecholamine (CAs) biosynthesis & physiological regulation in neuroendocrine cells has been reviewed. CAs in neuroendocrine cells is in state of constant flux. They are continuously being synthesized released & metabolized yet they maintain a remarkable constant level in tissues. The steps in the biosynthesis of CAs & related enzyme inhibitors are given below;

1. The first step in CA biosynthesis is the 3 hydroxylation of acid L-Tyrosine to form L-DOPA. L-Tyrosine is normally present in the circulation & transported actively into adrenergic neuron

where it is 3'hydroxylated by tyrosine hydroxylase (TH). As usual for the first enzyme in a biosynthetic pathway, TH hydroxylation is the rate limiting step in the biosynthesis of NE. This enzyme plays a key role in the regulations of CA biosynthesis & is therefore the logical biological target of some drugs.



2. The second step in CA biosynthesis is the decarboxylation of the L-DOPA to give DA. This is an important Neuotransmitter. The enzyme involved is DOPA decarboxylase. This enzyme is acts on all naturally occurring aromatic L-amino acids hence also referred as L-aromatic amino acid decarboxylase (AADC).

3. The third step in CA biosynthesis is side chain beta-hydroxylation of DA to give NE. DA formed in the cytoplasm of the neuron is actively transported in to storage vesicles & is then hydroxylated stereo specifically at beta carbon to NE inside the vesicle by dopamine B-hydroxylase (DBH). The NE-formed is stored in the vesicles until depolarization of the neuron initiates the process of vesicles fusion with the plasma membrane & squeeze NE into the synaptic cleft.

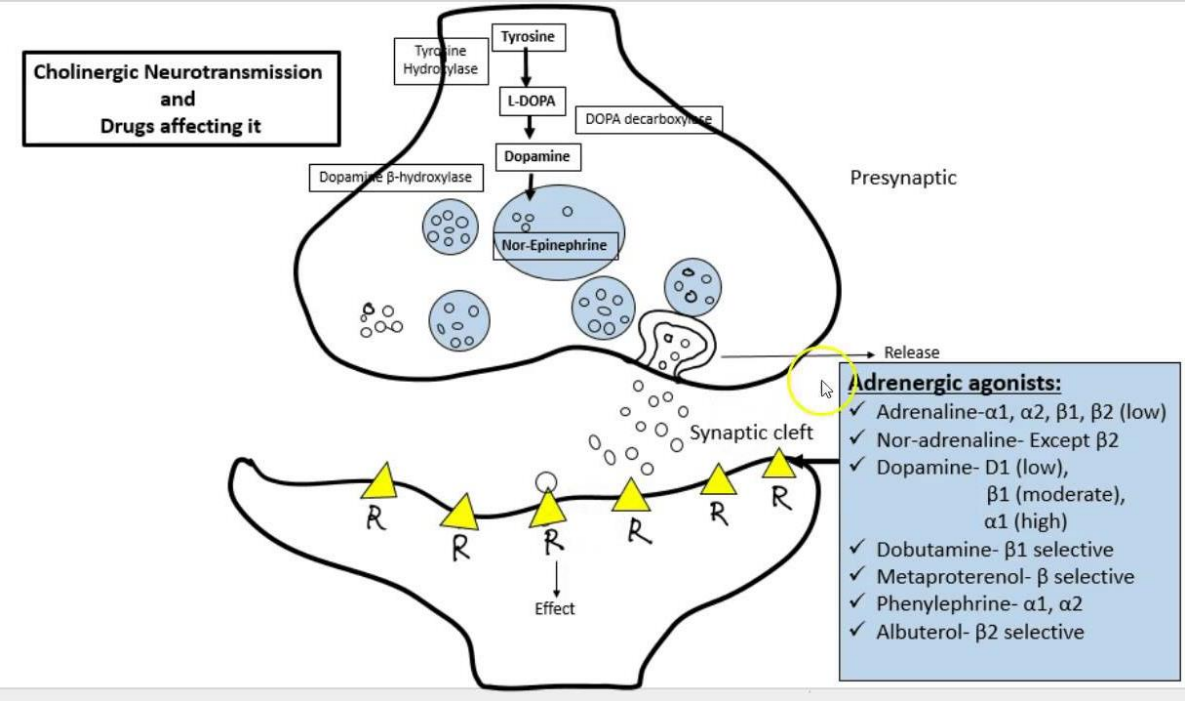
4. The last step in CA biosynthesis is the N methylation of NE to give E in the adrenal medulla. The reactions catalyzed by the enzyme phenylethanolamines N-methyl transferase (PNMT).

- A large percentage of the NE present is located within highly specialized subcellular particles in sympathetic nerve ending & chromaffin cells. Much of the NE in CNS located within similar vesicles.

- After its release NE diffuse through intercellular space to bind reversibly adrenoreceptors on effector cell triggers biochemical cascade that leads to physiological response once NE has exerted it's effect at adrenergic receptor, there must be mechanism for removing the NE from synapse & terminating its action at the receptors These mechanisms include:

- Upake1: 95% of released NE is removed from synapse. Part of it is metabolized be part transferred into storage vesicles again for use

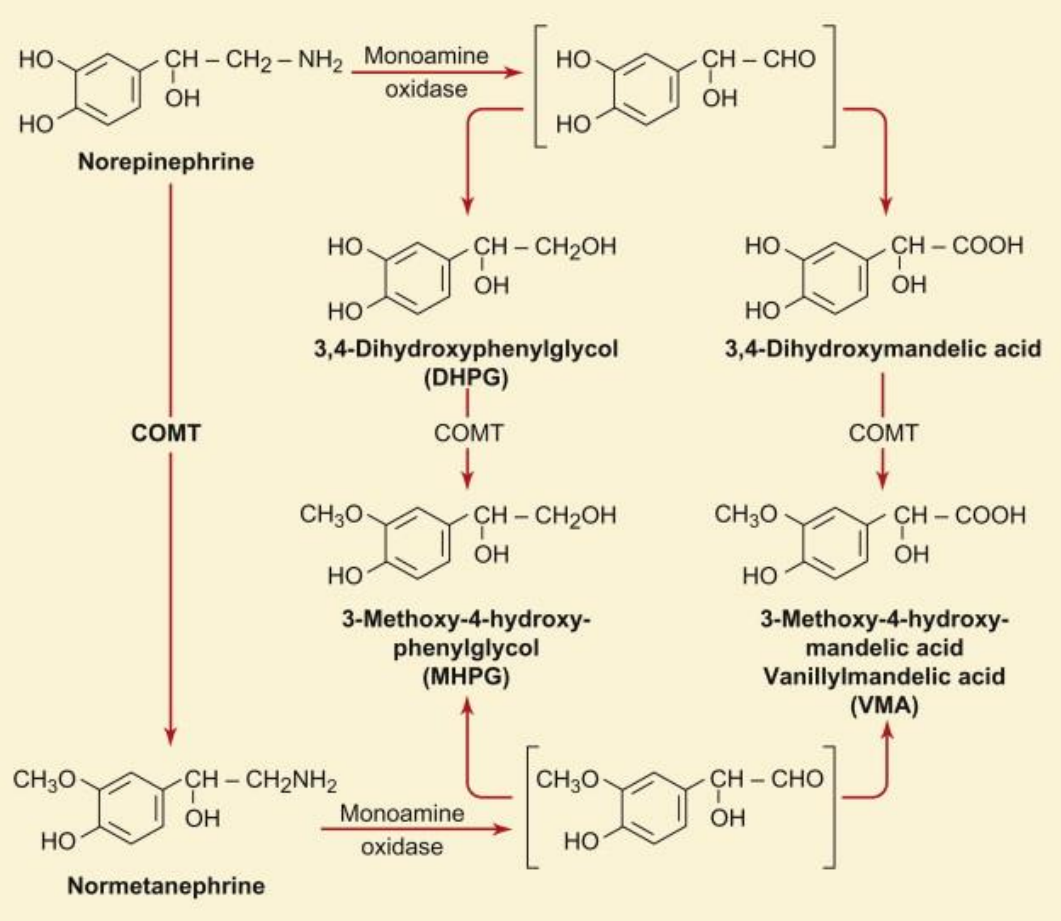
- Uptake-II rarely occurs, occurs when there is high concentration. Portion which released from uptake diffuses out in synapse and metabolized by various pathways.



METABOLISM

- The two major enzyme systems involved in the metabolism of catecholamine are monoamine oxidase (MAO) and catechol-o-methyl- transferase (COMT).A major mode of termination of the action of noradrenalin is by reuptake (80-90%) in to adrenergic neuron (uptake-1) to be reused as transmitter. The remainder is metabolized by MAO (oxidative deamination) & COMT (O-Methylation). The end products, vanillyl manadelic acid (VMA) and metanephrines are excreted in the urine.
- In addition to the specific neuronal uptake (Uptakt D mechanism for noradrenalin there is an extra neuronal uptake (Uptake-2) mechanics Uptake-2 operates only when high concentrations of catecholamine are circulating in the blood system. After transport by uptake-2, the catecholamines are not stored but are rapidly metabolized intracellularly by both COMT and MAO. MAO and COMT are widely distributed in the body, but only MAO is present in the

adrenergic neuron, It is likely that MAO mainly regulates the amount of NA stored intraneuronally, while COMT is mainly responsible for the inactivation of circulating catecholamines by methylation.



ADRENERGIC RECEPTORS (alpha & Beta) & THEIR DISTRIBUTION

In 1948 Ahlquist sub classified adrenergic receptors into alpha & Bea adrenoreceptors based on their responses to different adrenergic receptors. Adrenergic receptors are membrane bound receptors located throughout the body on neuronal & neuronal tissues where they mediate a diverse range of response. They are protein coupled receptors. There are two main groups of adrenergic receptors alpha & Beta with several subtypes:

Most tissues express multiple receptors. However, the dominant beta receptor in the normal heart is the beta 1 receptor while the beta 2 receptor is the dominant regulatory receptor in vascular and non-vascular smooth muscle. Epinephrine activates both the beta1 and beta 2 receptors while Norepinephrine activates only the beta1 -receptor.

- Effect of Beta 1 Receptor Activation on the Heart:

Activation of the beta 1 receptor leads to increases in contractile force and heart rate. Drugs that activate the beta 1 receptor can be used in heart failure to improve the contractile state of the failing heart. Drugs that activate the beta 1 receptor also increase heart rate. Indeed, excess stimulation the beta 1 receptor can induce significant increases in heart rate and arrhythmias. Arrhythmias are a major concern with drugs such as epinephrine hat can be absorbed systemically after intra-oral injection.

- Effect of Beta 2 Receptor Activation on Smooth Muscle:

Activation of the beta 2 recepti leads to vascular and nonvascular smooth muscle relaxation Drugs that activate the b receptor can be used to treat asthma (by relaxing airway smooth muscle) and Premature labor (by relaxing uterine smooth muscle).

- Beta 3 receptors are present in adipose tissue & are thought to role in the regulation of lipid metabolism.

- Postsynaptic Alpha Receptors on Vascular Smooth Muscle:

Associated with vascular smooth muscle are a large number of alpha1 receptors relative to beta 2 receptors. Activation of these receptors by sympathetic nervous system transmission de drugs will result in vasoconstriction and an increase in peripheral resistance and system arterial blood pressure.

- Presynaptic Alpha Receptors:

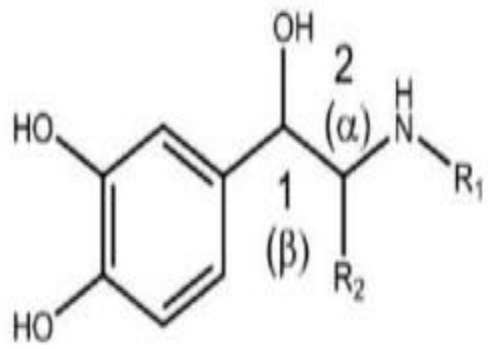
Alpha 2 receptors also exist presynaptically associated with nerve terminals. Activation of these receptors inhibits the release of norepinephrine. Norepinephrine acts at presynaptic alpha2 receptors to inhibit its own release.
Both epinephrine and norepinephrine activates both the alpha1 and alpha2 receptors

SYMPATHOMIMETIC AGENTS

Sympathomimetic agents produce effects resembling those produced by stimulation of the sympathetic nervous system. They may be classified as agents that produce effects by direct, indirect or mixed mechanism of action

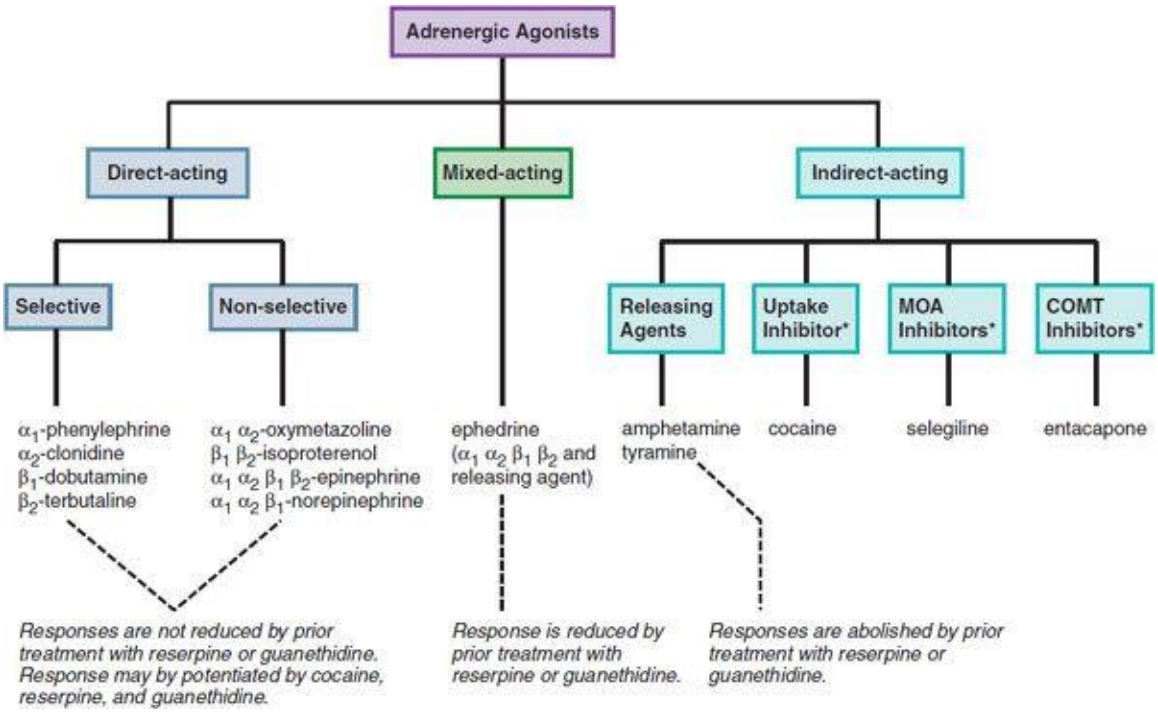
SAR of sympathomimetic Agents

The parent structure for many of sympathomimetic drug is B-phenylethylamine.



1) Maximum activity is seen in B-pheynylethylamine derivatives containing hydroxy! group in the meta and para positions.
2) Amino group separated by two carbon atoms from substituted benzene ring is minimally required for high agonist activity.
3) The presence of amino group in phenylethylamine is important for direct agonist activity
4) Both primary and secondary amines are found among the potent direct acting agonists but tertiary or quaternary amines tend to be poor direct agonists.
5) If we introduce methyl group at R_1 position activity at alpha receptor decreases and activity at Beta-receptor increases
6) Alpha-agonistic activity is dramatically decreases when R_1 is larger than methyl group.
7) Introduction of ethyl group on the carbon atom adjacent to the amino nitrogen diminishes alpha-activity far more than Beta activity.
8) Substitution on alpha carbon provides asymmetric carbon which provides di stereo isomers. For eg. Alpha -methyl norepinephrine has maximum direct activity.
9) Catechol moiety is an important structure feature in terms of yielding compounds with maximal agonistic activity at adrenergic receptors.

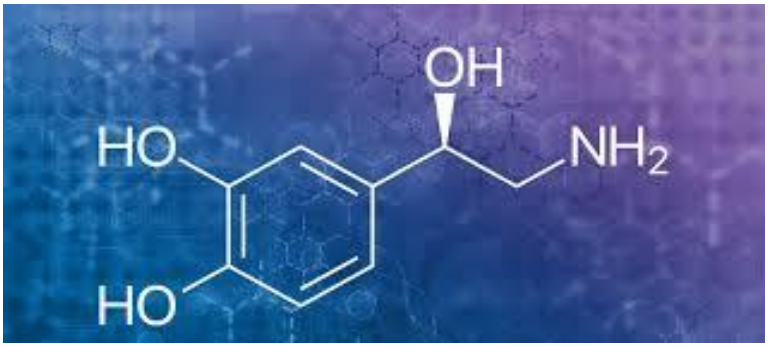
Classification of sympathomimetics



SYMPATHOMIMETICS (DIRECT ACTING)

Non-selective Adrenergic agonists

<u>Norepinephrine</u>



- *Mechanism of action*:

It performs its action by being released into the synaptic cleft, where it acts on adrenergic receptors predominantly on the alpha adrenoreceptors.

- Metabolism:

Norepinephrine rapidly metabolized by both COMT and MAO, resulting in poor oral bioavailability and short duration of action (1 or 2 minutes even when given intravenously).

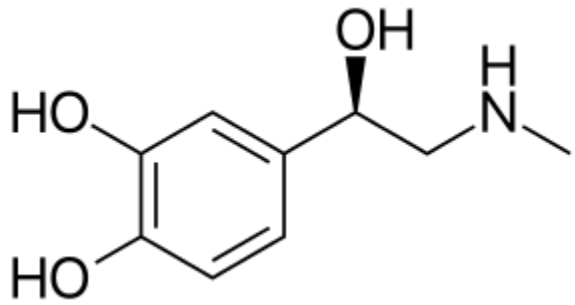
- Therapeutic uses:

It is used to counteract various hypotensive crises, because it's a activity raises blood pressure and as an adjunct treatment in cardiac arrest because its Beta- activity stimulates the heart. It has limited clinical application caused by non-selective nature of its activities.

- Adverse reactions:

Some dizziness or weakness may occur when taking norepinephrine. Also, an upset stomach and feelings of nervousness can occur. Pain, burning, irritation, or skin changes around the injection site, numbness, weakness, or cold feeling, slow or uneven heart rate, trouble breathing, vision, speech, or balance difficulties, spotted skin.

Epinephrine



- *Mechanism of action*:

It binds with adrenergic receptors which results in metabolic changes when it binds to a-adrenergic receptors.

- Metabolism:

The metabolic action of epinephrine leads to formation of 35 - adenosine monophosphate (C-AMP), which is the energy controlling reaction in effector cells.

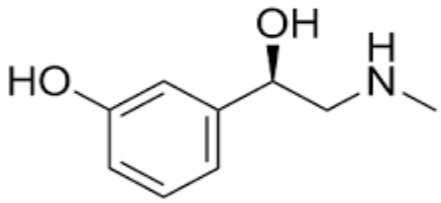
- Therapeutic Uses:

It is much more widely used clinically than NE. Epinephrine is us following conditions bronchial asthma, hypersensitivity reactions, heart block cardiac arrest, control of bleeding frequently added to local anaesthetic like lignocaine

- Adverse reactions:

The most common ill effects of epinephrine are anxiety, to tachycardia, palpitation, tremors restlessness, headache, acute pulmonary oedema etc.

Phenylephrine



Phenylephrine differs from epinephrine only in lacking a p-OH group.

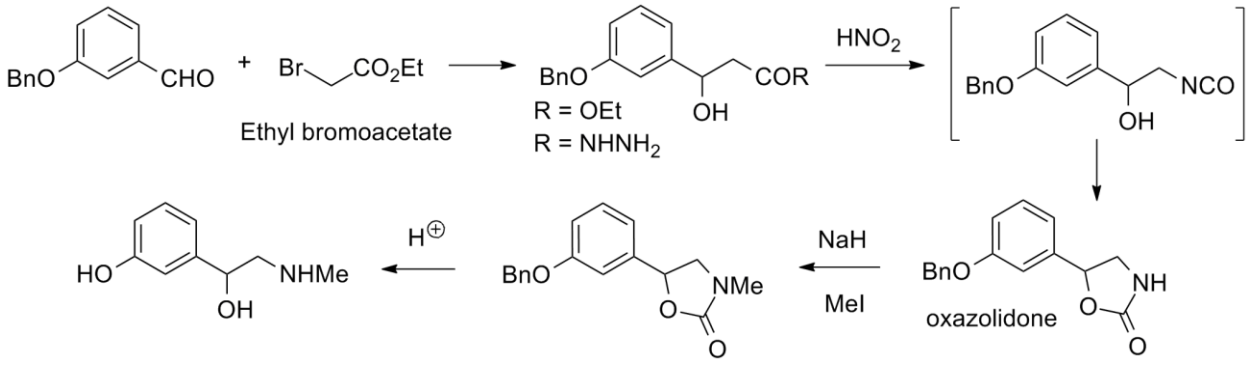
- *Mechanism of action*:

It is selective direct acting as - receptor agonist. It is potent vasoconstrictor but less potent than epinephrine.

- Metabolism:

Metabolized by MAO (Monoamino-oxidose) and it lacks catechol moiety hence not metabolized by COMT

- Synthesis:



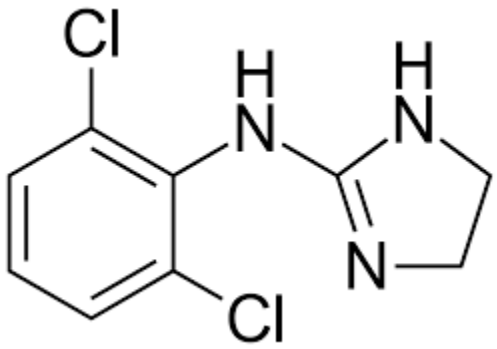
- Therapeutic uses:

It is used in the treatment of severe hypotension. It is selective a, - agonist and widely used as non-prescription nasal decongestant, used to treat open angle glaucoma

- Adverse reactions:

Hypertension and prostatic hyperplasia

Clonidine



- *Mechanism of action***:**

Clonidine can briefly exhibit vasoconstrictive activity as a result of stimulation of peripheral a-adrenergic receptors. Stimulation of az- receptors brings about decrease in sympathetic out flux from CNS which in turn leads to decrease in peripheral vascular resistance and blood pressure.

- SAR

1. Structurally imidazolines for the most part have the heterocyclic imidazoline nucleus linked to a substituted aromatic moiety via a bridging unit.
2. Although modification of the imidazoline ring generally results in compounds with significantly reduced agonistic activity
3. Open ring imidazolines are highly active
4. The optimum bridging unit (X) is usually a single amino methylene group
5. Agonistic activity is enhanced when the aromatic ring substituted with halogen substitutes like Cl or small alkyl groups like methyl, particularly when they are placed in the two ortho positions

- Metabolism:

Less than half of the absorbed portion of an orally administered dose will be metabolized by the liver into inactive metabolites, with roughly the other half being excreted unchanged by the kidneys.

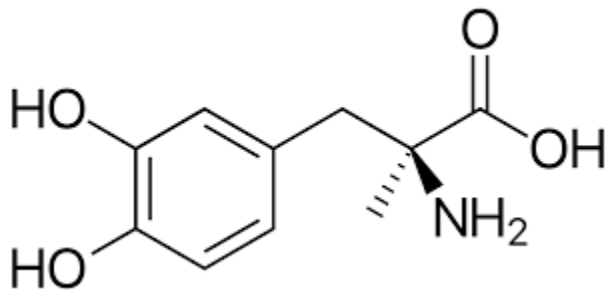
About one-fifth of an oral dose will not be absorbed, and is thus excreted in the faeces. The half-life of clonidine varies widely, with estimates between 6 and 23 hours, and is greatly affected by and prolonged in the setting of poor kidney function

- Therapeutic uses.

Treated structurally to imidazoline nasal decongestants originally synthesized as vasoconstriction nasal decongestants but after that found to have dramatic hypotensive effects.

- Adverse reactions: The common side effects are anxiety, constipation, sedation and rare side effects are hallucination, nightmare and itching.

Methyldopa –



Differs structurally from L-DOPA only in the presence of a alpha - methyl group.

- *Mechanism of action*:

It is originally synthesized as an L-Aromatic Amino Acid Decarboxylase (AADC) inhibitor. However it's mechanism of action is not caused by inhibition of AADC but rather by its metabolism in CNS to its active metabolite a- methyl norepinephrine.

- Metabolism:

Methyldopa converted to a - methyl dopamine by the enzyme AADC which further converted to a-methyl norepinephrine by the enzyme dopamine B hydroxylase.

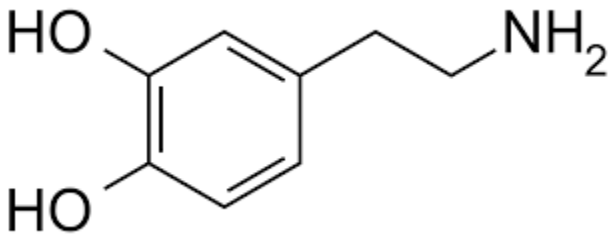
- Therapeutic Uses:

It is used in clinical treatment of hypertension pre-eclampsia.

- Adverse Reactions:

Dizziness, agitation, dry mouth, migraine and sedation.

Dopamine



Dopamine differs from NE in lacking of 1-OH group

- *Mechanism of action*:

Dopamine is naturally occurring catecholamine and has a neuro transmitter function in CNS. It exerts alpha adrenergic vasoconstrictor activity. Through beta adrenoreceptor stimulation dopamine increases myocardial contractility. Thus dopamine is a catecholamine which is unique in having a mixed action.

- Metabolism:

Dopamine rapidly metabolized by COMT and MAO. The end products are different than those of adrenaline and noradrenaline. They are excreted in urine.

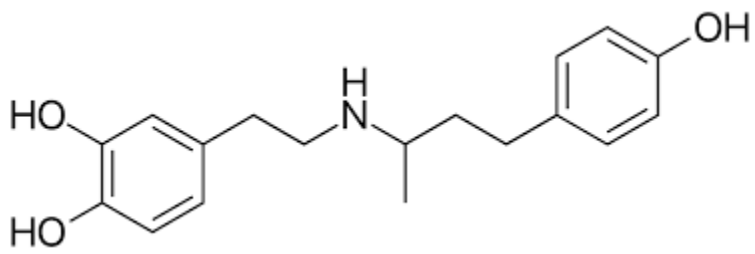
- Therapeutic Uses:

It is recommended for the treatment of shock resulting from trauma, surgery and myocardial infarction also used in the treatment of congestive heart failure, renal and liver failure.

- Adverse Reactions:

Toxic effects include nausea, vomiting, tachycardia and ectopic beats. Occasionally hypertension may develop.

Dobutamine



It resembles dopamine structurally but possesses a bulky 1-(methyl)-3-(4-hydroxy phenyl)propyl group on the amino group.

- *Mechanism of action*:

Dobutamine is synthetic direct acting sympathomimetics and is potent agonist of Beta-adrenoreceptor.

- Metabolism:

Dobutamine is metabolized by COMT and conjugation but not by MAO.

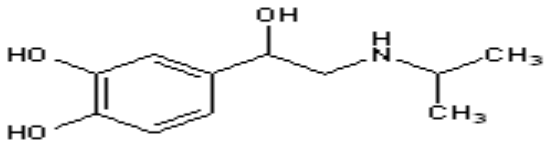
- Therapeutic Uses:

It is used in the treatment of congestive heart failure. Dobutamine more useful than dopamine in the treatment of cardiogenic shock.

- Adverse reaction:

Premature ventricular beats occur in 5% of patients, hypertension, angina pain, arrhythmia, nausea, and headache.

Isoproterenol (Isoprenalin)



It is synthetic catecholamine derived from noradrenalin by substitution of an isopropyl group on the nitrogen atom of aliphatic side chain.

- *Mechanism of action*:

The pharmacological actions of isoprenalin are due to its powerful beta stimulant activity and it has almost no action on alpha receptors

- Metabolism:

It is metabolized by COMT, sulphate and glucuronide conjugation.

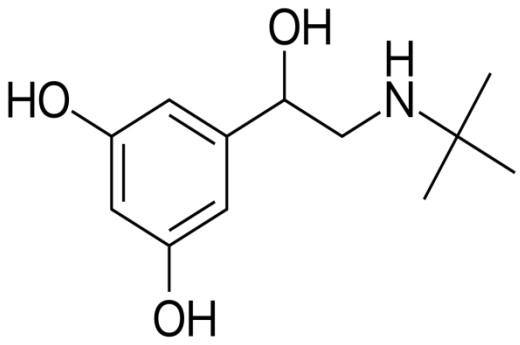
- Therapeutic uses:

It is used in treatment of moderate to severe attack of bronchial asthma. It is potent cardiac stimulant and hence useful for immediate treatment of heart block. Isoprenalin may be employed in cardiogenic shock.

- Adverse reactions:

Isoproterenol may cause palpitation, tachycardia, headache and flushing of skin, serious arrhythmias, angina pain, tremors, dizziness and sweating occasionally occur.

Terbutalin



It belongs to the structural class of resorcinol bronchodilators that have 3’5'-di-OH group of the phenyl ring

- *Mechanism of action*

A 3’5’-di-OH group confers beta 2 receptor selectively on compounds with a large amino substitute. They relax the bronchial muscle.

- Metabolism:

Terbutalin resistant to metabolism by either COMT or MAO. Instead, its metabolism primarily involves glucuronide conjugation.

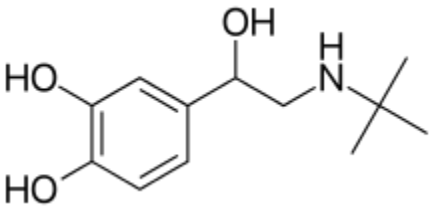
- Therapeutic uses:

Used in patients with asthma but cause less direct cardiac stimulation.

- Adverse reactions:

Common side effects of terbutaline include: Tremor, nervousness dizziness, headache, drowsiness, palpitations, rapid heart rate, shortness of breath, chest discomfort, nausea, vomiting, weakness, flushed feeling, sweating, pain at the injection site, anxiety, muscle cramps, and dry mouth.

Bitolterol



It defers from isoprenalin by replacing the N- isopropyl to beta 2 directing N-ter-butyl group.

- *Mechanism of action*

Bitolteral is a type of Beta 2 adrenergic agonist. When Beta adrenergic receptor are activated its activation results in relaxation of smooth muscle in the lung and dilation and opening of the airways which make airflow easy through the tubes.

- Metabolism:

It is prodrug of colterol in which catechol hydroxyl groups converted to 4 methyl benzoic acid ester. This ester is cleaved by esterase to colterol which is subjected to metabolism by COMT

- Therapeutic uses:

It is used for the relief of bronchospasm in condition like COPD and asthmas.

- Adverse reactions:

Cough, dry Mouth, high Blood Pressure, irritation of the larger a passages of the lungs, mouth irritation, nervous, taste problems, temporary redness of face and neck.

Adrenergic Receptor Agonists

All selective alpha 1 agonists have therapeutic activity as vasoconstrictors. Structurally they include 2-arylimidazolines such as xylometazoline, oxymetazoline, tetrahydrozoline and naphazoline.

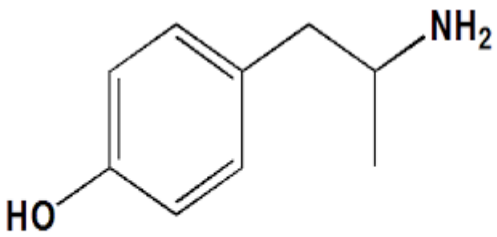
These agents are used for their vasoconstrictive effects as nasal and ophthalmic decongestants. All 2 arylimidazol alpha1 - agonist contain one carbon bridge between C-2 of imidazoline ring and a phenyl ring, and thus a phenylethyl amine structure feature is there. Ortho-lipophilic groups on the phenyl ring are impotant for alpha - activity. However, Meta or para-bulky lipophilic substituents on the phenyl ning may be important for the alpha1-selectivity. They have limited access to the CNS. Xylometazoline and oxymetazoline have been used as topical nasal decongestants because of their ability to promote constriction of nasal mucosa. When taken in large doses, oxymetazoline may cause hypertension

INDIRECT ACTING AGENTS

Indirect acting sympathomimetics act by releasing endogenous NE. They also enter the nerve ending by the way of the active uptake process and displace NE from its storage granules.

Hydroxyamphetamine:

It is an effective indirect acting sympathomimetic drug. The presence of beta-hydroxyl group decreases and alpha-methyl group increases effectiveness of indirect acting agents.



hydroxyamphetamine

- Mechanism of action:

It stimulates the norepinephrine which releases from central adrenergic receptors. Hydroxyl - amphetamines in periphery causes the release of noradrenaline when it acts on the adrenergic nerve terminals, alpha and B receptors.

- Metabolism:

In humans, amphetamine is metabolized to 4-hydroxyamphetamine by CYP2D6, which is a member of the cytochrome P450 superfamily and is found in the liver. 4-Hydroxyamphetamine is the metabolized by dopamine beta-hydroxylase into 4-hydroxynorephedrine or eliminated in the urine

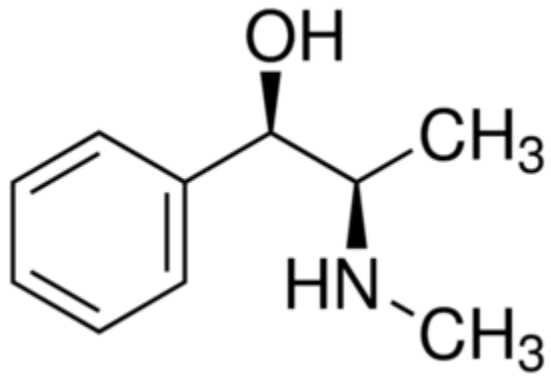
- Therapeutic uses:

It is used to dilate the pupil for diagnostic eye examinations and for surgical procedures on the eye. It is employed in the treatment of narcolepsy, depressive states, motion sickness and obesity.

- Adverse reactions:

It may induce dryness of mouth, restlessness, insomnia, anorexia. With higher dose there may be hypertension, tachycardia, angina pain and cardiac arrhythmia.

• Pseudoephedrine



It is the (S, S) diastereoisomer of ephedrine.

- Mechanism of action:

Ephedrine has a mixed mechanism of action, L-(+) pseudoephedrine acts mostly by an indirect mechanism and has virtually no direct activity

- Metabolism:

Incompletely metabolized in liver by N -demethylation to inactive compounds. Excretion: 55% to 75% of dose excreted unchanged in urine remainder excreted as unchanged drug and metabolites.

- Therapeutic uses:

L-(+) pseudoephedrine's lack of direct activity affords fewer CNS effects than does ephedrine. This agent is found in many OTC nasal decongestants and cold medications.

- Adverse Reactions:

Common adverse drug reactions (ADRS) associated with pseudoephedrine therapy include central nervous system stimulation, insomnia, nervousness, excitability, dizziness and anxiety. Infrequent ADRs include tachycardia or palpitations. Rarely, pseudoephedrine therapy may be associated with mydriasis (dilated pupils), hallucinations, arrhythmias, hypertension, seizures and ischemic colitis, as well as severe skin reactions known as recurrent pseudo-scarlatina, systemic contact dermatitis etc.

Propylhexedrine

It is another analog of amphetamine in which the aromatic ring has been replaced with cyclohexane ring

- Mechanism of action:

This drug produces vasoconstriction and a decongestant effect on the nasal membranes. It produces fewer effects on the CNS.

- Metabolism:

Propylhexedrine undergoes metabolism to form vanous metabolites including norpropylhexedrine, cyclohexylacetoxime, cis and trans-4-hydroxy- propylhexedrine

- Therapeutic uses:

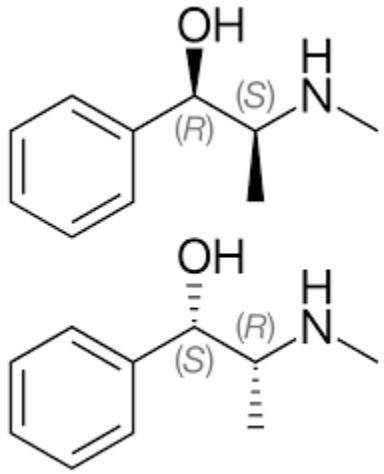
It's major use is for local vasoconstrictive on nasal mucosa in the symptomatic relief of nasal congestion caused by the common cold, allergic rhinitis or sinusitis

- Adverse reactions:

Burning, stinging, sneezing increase in nasal discharge.

AGENTS WITH MIXED MECHANISM

Ephedrine



Ephedrine is one of the example of phenylethylamine considered to have mixed mechanism of action usually have no hydroxyl on aromatic ring but do have a ß-hydroxyl group.

- Mechanism of action:

The drug acts on both alpha and Beta receptors. It is the classic example of a sympathomimetic with a mixed mechanism of action.

SAR:

1. Ephedrine has two asymmetric carbon atoms, thus there are four optically active forms. The erythro racemate is called ephedrine and threo racemate known as pseudoephedrine.
2. Natural ephedrine is the D-isomer and it is the most active of the four isomers.
3. Lacking H-bonding phenolic OH group, ephedrine is less polar and thus crosses the BBB (Blood Brain Barrier).
4. This isomer has the correct (R) configuration at the carbon atom bearing the hydroxyl group and the desired (S) configuration at the carbon bearing methyl group for optimum direct activity.
5. Ephedrine does not have any phenolic substituents on the phenyl ring giving it a mixed acting response.

- Metabolism:

The drug is not metabolized by either MAO or COMT. Rather it is P- hydroxylated and N-demethylated by cytochrome, P450 mixed function oxidases.

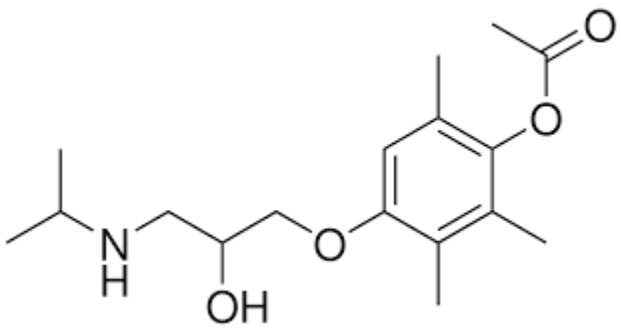
- Therapeutic Uses:

Ephedrine and its salts are used orally intravenously and topically a variety of conditions such as allergic disorders cold, hypotensive conditions and narcolepsy.

- Adverse reactions:

Arrhythmia, anxiety, tachycardia, headache, hypertension, acute pulmonary edema, panic attack.

Metaraminol



- Mechanism of action:

Metarminol selective for receptors have little cardiac stimulant action. It is used for hypotension.

- Metabolism:

It lacks catecol moiety and thus is not metabolized by COMT. Intestinal 3' O glucuronidation, sulphation and metabolism by MAO.

- Therapeutic uses:

It has widespread use as a non-prescription nasal decongestant, reduces congestion and swelling by constricting blood vessel of the membranes. In a eye, it is used to dilate pupil and to treat open angle glaucoma. It is used in spinal anesthesia.

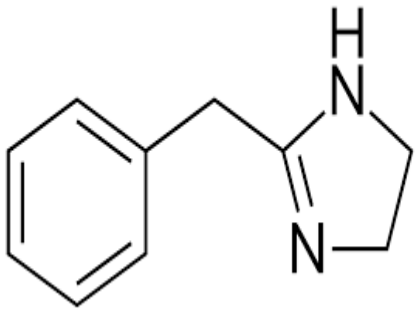
- Adverse reactions:

It is relatively non-toxic and produces little CNS stimulation.

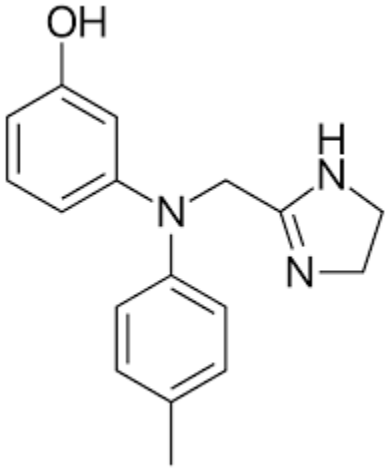
ADRENERGIC ANTAGONISTS

ALPHA ADRENERGIC BLOCKERS

• Non-selective alpha - adrenergic antagonists
Eg. **Tolazoline and Phentolamine**



Tolazoline



Phentolamine

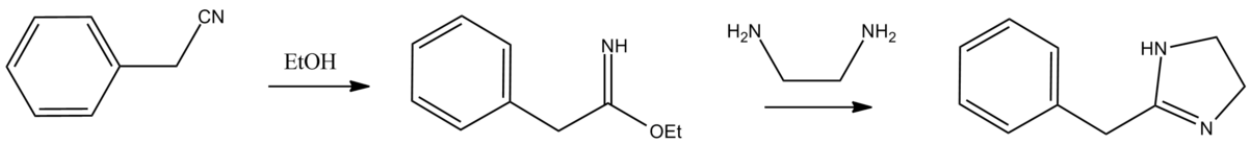
- Mechanism of action:

Tolazoline and phentolamine have both alpha 1 and alpha 2 blocking activity and produce tachycardia. The blocking action of these agents at presynaptic alpha 2 - receptors, contributes to their cardiac stimulatory effects by enhancing release of NE.

- SAR:

1. The agents in this class are structurally similar to the imidazoline alpha - agonist and the type of group attached to the imidazoline ring dictates whether it is agonist or antagonist.
2 For alpha 1 - agonists SAR studies extensive molecular modelling studies have been provided.
3. Phentalamine is more effective alpha- antagonists while the antagonistic action of tolazoline relatively weak.

- Synthesis



Benzyl cyanide iminoether Tolazoline

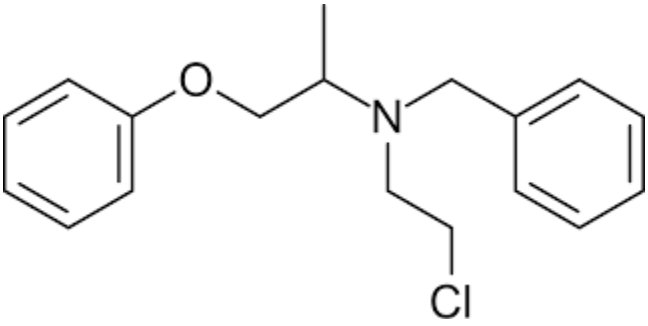
- Therapeutic uses:

Tolazoline is used to increase blood flow in peripheral vasospastic condition like Raynaud's syndrome. Tolazoline used in persistent pulmonary hypertension of the newborn. Phentalomine is used to prevent or control hypertensive episodes.

- Adverse reaction:

Tachycardia increased gastrointestinal motility and hyperchlorhydria.

Phenoxybenzamine



Phenoxybenzamine is the only haloalkylamine in clinical use at present.

- Mechanism of action:

They are irreversible blockers of alpha - adrenergic receptors. Chemically it is a Beta - haloalkylamine produce a long lasting, irreversible a - adrenergic blockade. Initial step involves the formation of an intermediate aziridinium ion which will form reversible complex with the receptor. The positively charge aziridinium ion electrophile then reacts with a nucleophilic group on the receptor resulting in the formation of covalent bond between the drug receptor which will lead to alkylated receptor.

- Metabolism:

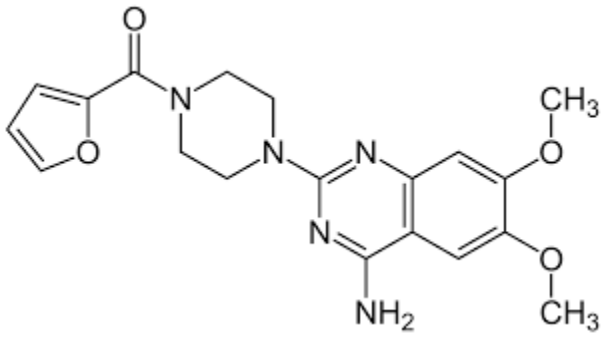
Phenoxybenzamine is very lipid soluble. It is metabolized (dealkylated) in the liver and excreted in bile and urine. It causes local irritation and therefore can only be administered intravenously or orally.

- Therapeutic Uses:

Phenoxybenzamine is used to treat peripheral vasospastic conditions like Raynaud's disease, used in treatment of hypertension.

- Adverse Reaction: Side effects include nasal congestion, bronchaconstriction and miosis, reflex tachycardia, congestive heart failure, cerebral stroke or kidney failure.

Selective a- blockers
Prazosin



Prazosin is quinazoline alpha 1 - blocker. As a result of its greater alpha 1 - receptor selectively, the quinazoline class of a-blockers exhibits greater clinical utility.

- Mechanism of action:

It has potent alpha 1 - adrenoreceptor blocking activity. It is potent and effective antihypertensive agent and maybe usefully combined with the beta- adrenoreceptor blockers, and thiazide diuretics.

- SAR:
  1. Structurally prazosin consists of three components - the quinazolme ring the piperazine ring and acyl moieity
  2. The 4- amino group on quinazolin ring is very important for a receptor affinity.
  3. The piperazine moiety can be replaced with other heterocyclic moieties (eg piperidine moiety) without loss of affinity.
  4. The nature of the acyl group has a significant effect on the pharmacokinetic properties

- Metabolism:

Prazosin is extensively metabolised by the liver and has high first-pass metabolism and low oral bioavailability.

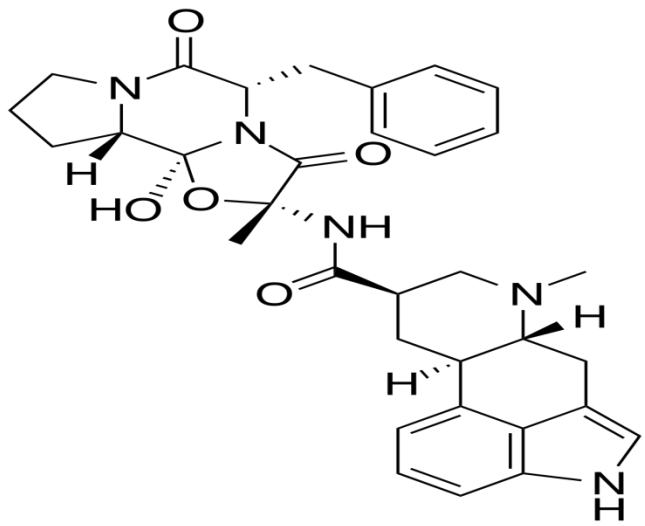
- Therapeutic Uses:

Used in treatment of hypertension and heart attack. Also help to improve urination flow rate.

- Adverse Reactions:

Side effects of prazosin are nasal congestion, dizziness, tiredness, nausea, drowsiness, blurred vision, orthostatic hypotension

Dihydroergotamine



Ergot is a parasitic fungus on rye and certain grains. Two major actions of ergot alkaloids are : to stimulate smooth muscles and to block alpha- adrenoceptors.

- Mechanism of action

Dihydroergotamine increases the a - blocking potency and reduces the smooth muscle stimulant activity.

- Metabolism:

Metabolism of dihydroergotamine by a cytochrome P-450 similar to that involved in the metabolism of macrolide antibiotics.

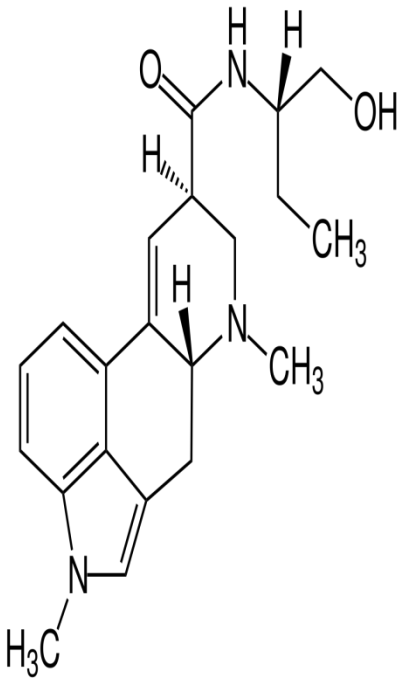
- Therapeutic uses:

Dihydroergotamine used to treat migraine. The pain of migraine and vascular headache is associated with vasodilation, odema, hydroergotamine is effective due to its action on vascular smooth muscle and should be given during vasoconstriction phase.

- Adverse reaction:

Nausea is a common side effect of IV administration and less common in other modes. Antiemetics can be given prior to DHE to counteract the nausea. Risks and contraindications are similar to the triptans. DHE and triptans should never be taken within 24 hours of each other due to the potential for coronary artery vasospasm. DHE produces no dependence. Vomiting blurred vision, nasal stiffness.

Methylsergide



It is structurally identical to methyl ergonovine except methyl group to indole nitrogen. All ergot alkaloids are amide derivative of lysergic acid but diethyl amine lysergic acid produce profound hallucinatory effect.

- Mechanism of action

Methysergide interacts with serotonin (5-HT) receptors. Its therapeutic effect in migraine prophylaxis has been associated with its antagonism at the 5-HT2B receptor. It is an antagonist at the 5-HT2C receptor, while at the 5-HTIA receptor it serves as a partial agonist. It is known to have partial agonist effects on some of the other 5-HT receptors as well.

It antagonizes the effects of serotonin in blood vessels and gastrointestinal, smooth muscle, but has few of the properties of other ergot alkaloids.

- Metabolism:

Methysergide is metabolized into methylergometrine in humans, which is responsible for its psychedelic effects. The systemic availability of methysergide was only 13%, most probably due to a high degree of first-pass metabolism to methylergometrine

- Therapeutic uses:

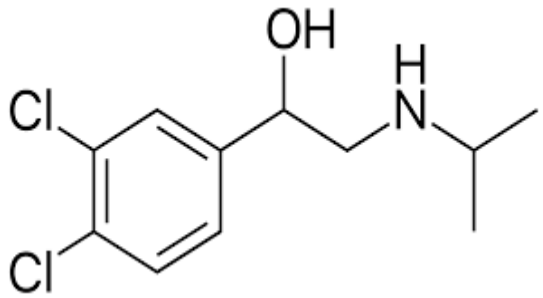
It is used to treat headache, carcinoid syndrome and serotonin syndrome.

- Adverse reactions.

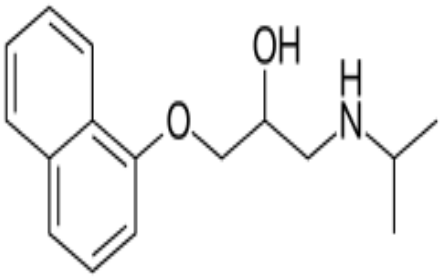
Its common side effect is retroperitoneal fibrosis. Rare effects are pleural and subendocardial fibrosis.

Beta-Adrenergic blockers

Beta - blockers are among the most widely employed antihypertensive and are also considered the first line treatment for glaucoma. Most of the B-blockers are in the chemical class of aryloxypropanolamines. The first B- blocker, dichloroisoproterenol was reported in 1958.



Dichloroisoproterenol



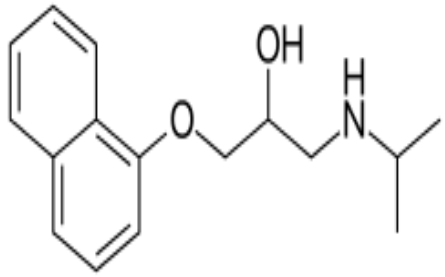
Propanolol

- SAR of Beta-blocker

1. Dichloroisoproterenol differs from isoproterenol in that the agonist directing 3'4-diOH groups have been replaced by two chloro groups but DC1 is not a pure antagonist but partial agonist.
2. Propranolol is the standard against which all other B-blockers compared. It consists of OCH_2 group which incorporated between the aromatic ring & the ethylamine side chain
3. OCH_2 group is responsible for the antagonistic property of the molecules. However it is not true because several compounds contain - OCH2 group are potent Beta-agonist.
4. The aryl group also affects the absorption, excretion & metabolism of B-blockers.
5. The nature of the aromatic ring is also a determinant in their Beta 1 selectivity.
6. One common structural feature of many cardioselective Beta-blocker is the presence of a para substitution of sufficient size on the aromatic ring along the absence of meta substituents e.g. Proctolol
7. For B-blockers, the B-OH substituted carbon must be in the S absolute configuration for maximal B-blocking activity.
8. Propranolol & most other B-blockers are used clinically as racemic mixtures. The only exceptions are levobunolol, timolol & penbutolol with which the (S) enantiomer is used.
9. The branched & bulky N-alkyl functional moieties such as ter-butyl, iso-propyl etc. proved to be extremely vital for B-antagonistic activity.
10. The alcoholic function on side chain is an absolute necessary requirement for its activity.
11. Isosteric replacement of the ethereal linkage (-O-) with moieties such as CH_2 S or NCH_3 found to be more or less detrimental.
12. The amine nitrogen should always be a secondary in character with regards to the optimum activity.

Non Selective blockers

Propranolol



- Mechanism of action

It is prototypical & non selective p-blockers. It blocks the beta 1 & Beta 2 receptors with equal affinity

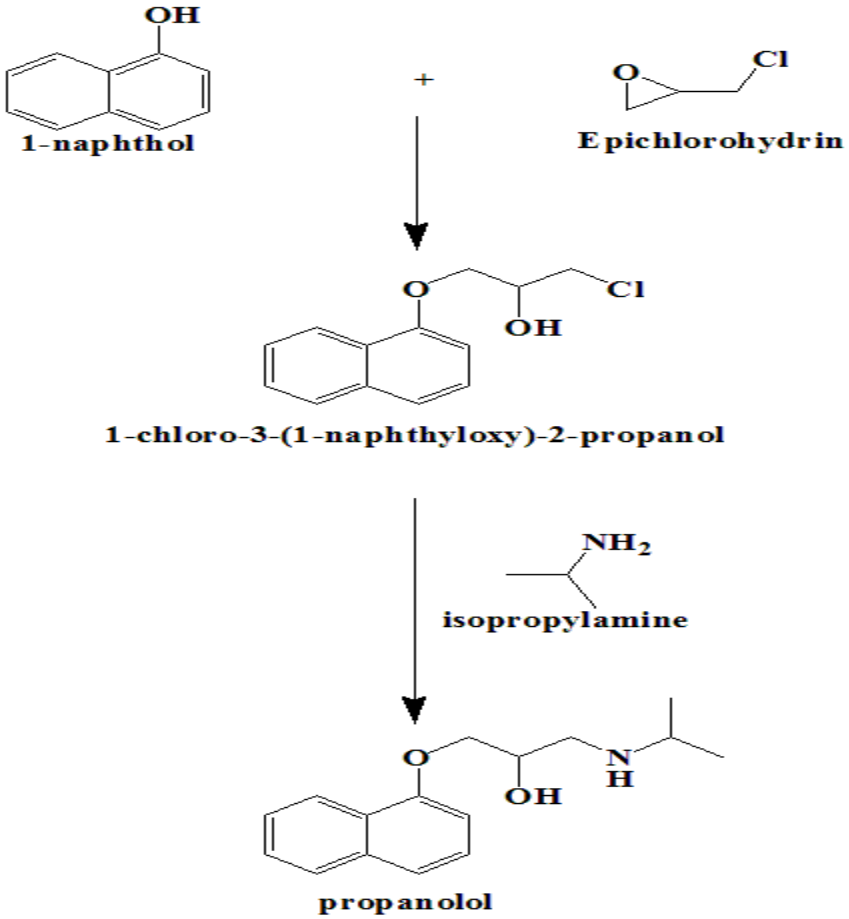
SAR:

1. Lengthening of side chain prevent appropriate binding of required functional group to same receptor site
2. Propranolol is the most lipophilic drug among the available B-blockers.

- Metabolism:

It undergoes extensive first pass metabolism one of the major metabolite of propranolol is mephthoxylactic acid. It is formed by metabolic reactions involving N- dealkylation, deamination & oxidation of the resultant aldehyde.

- Synthesis:



- Therapeutic uses:

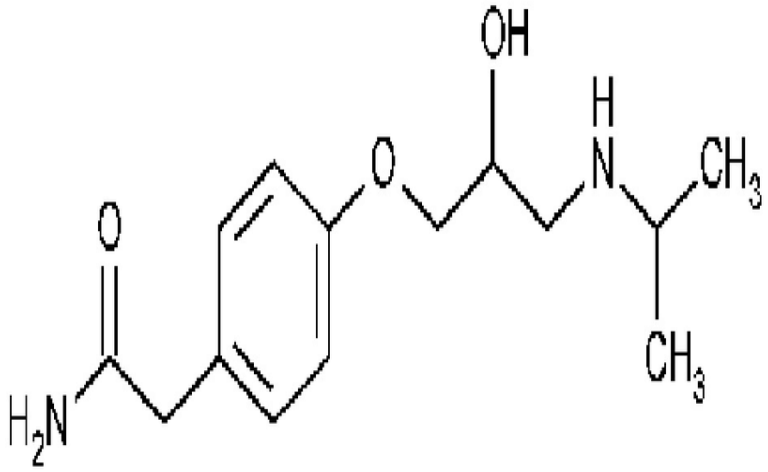
Propranolol approved for use in angina pectoris, past myocardia infarction, hypertension, cardiac, migraine prophylaxis & essential tremor also used in CNS disorders.

Adverse reactions: Sleep disturbance like insomnia and nightmares. Propranolol should be used with caution in people with:

Diabetes mellitus or hyperthyroidism since and symptoms of hypoglycemia may be masked.

Peripheral vascular disease and Raynaud's syndrome, which may be exacerbated Phaeochromocytoma, as hypertension may be aggravated without prior alpha blocker therapy.

Atenolol



- Mechanism of action

It is a type of selective B1 receptors antagonist, a drug belonging to the group of ß blocker used in treatment of cardiovascular diseases & hypertension.

- Metabolism:

Atenolol undergoes little or no metabolism by the liver and the absorbed portion is eliminated by renal excretion Over 85% of intravenous dose is excreted in urine within 24 hours compared with 50% for an oral dose.

- Therapeutic uses:

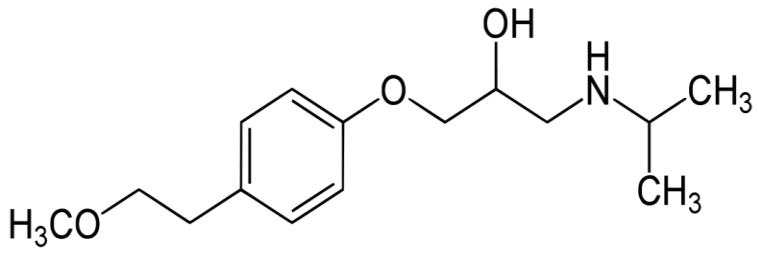
Atenolol is used for a number of conditions including hypertension, angina, long QT syndrome, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, and the symptoms of alcohol withdrawal.

- Adverse reactions:

Atenolol was the main B-blocker identified as carrying a higher risk of provoking type 2 diabetes, leading to its downgrading in the United Kingdom in June 2006 to fourth-line agent in the management of hypertension.

Antihypertensive therapy with atenolol provides weaker protective action against cardiovascular complications myocardial infarction stroke) compared to other antihypertensive drugs. In some cases, and are superior. In addition, atenolol has been found to lack mortality benefits and even to increase mortality in older adults.

Metoprolol



- Mechanism of action

Metoprolol blocks Beta 1 adrenergic receptors in heart muscle cells, thereby decreasing the slope of phase 4 in the nodal action potential (reducing Na+ uptake) and prolonging repolarization of phase 3 (slowing down K+ release). It also suppresses the norepinephrine-induced increase in the sarcoplasmic reticulum (SR) Ca2+ leak and the spontaneous SR Ca2+ release, which are the major triggers for atrial fibrillation

- SAR:

1. The presence of para substitute of sufficient size on the aromatic ring along with absence of Meta substitute is one of the common structural features of Beta 1-adrenoreceptor antagonist.

2. 4-substituted aryloxypropanolamines are selective B1 blockers.

- Metabolism:

It undergoes a-hydroxylation and O-demethylation as a substrate of the cytochrome liver enzymes CYP2D6 and a small percentage by CYP3A4, resulting in inactive metabolites.

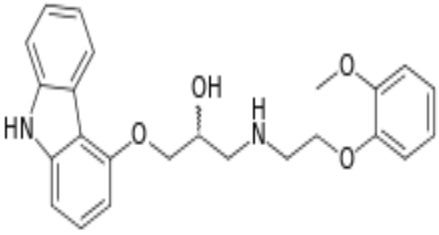
- Therapeutic uses:

It is used in treatment of hypertension, acute myocardial infarction, angina supraventricular & ventricular tachycardia. It is also used in treatment of migraine headaches & congestive heart failure.

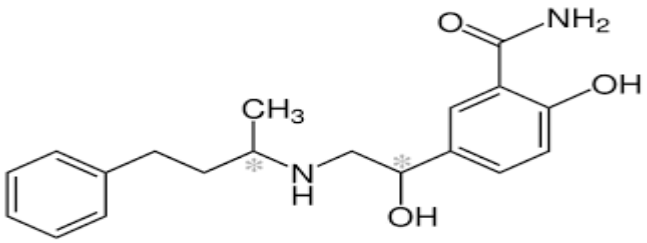
- Adverse reactions:

Side effects, especially with higher doses, include dizziness, drowsiness, fatigue, diarrhea, unusual dreams, trouble sleeping, depression, and vision problems. Metoprolol may also reduce blood flow to the hands or feet, causing them to feel numb and cold; smoking may worsen this effect. Due to the high penetration across the blood-brain barrier, lipophilic beta blockers such as propranolol and metoprolol are more likely than other less lipophilic beta blockers to cause sleep disturbances such insomnia and vivid dreams and nightmares.

Mixed alpha/beta Adrenergic Antagonist
Labetalol and Carvedilol



Carvedilol



Labetalol

- **Mechanism of action**: Both drugs are antihypertensive with al, B1 & B2 blocking activity.
- SAR

1. If we replace t-butyl or isopropyl group of alpha 1 -receptor agonist by larger groups the agonistic activity decreases and antagonistic activity increases.
2. Carvedilol has an estimated Beta blocking activity 10-100 times it's a- blocking activity.
3. Labetalol has more potent Beta-antagonist than alpha-agonist & it has two asymmetric carbon atoms & it exists as a mixture of four isomers.
4. In labetalol Beta-blocking activity shown by (1R, 1'R) isomers alpha l -antagonistic activity shown by (1S, 1'R) isomers. Greater activity showed by (1S, 1'R) isomers.
5. Carvedilol is Beta blocker that possesses alpha -adrenergic receptor blocking activity & only (S) enantiomer possesses the Beta-blocking activity.

While both enantiomers are antagonists of alpha 1 -receptor.

- Metabolism:

Carvedilol is about 25% to 35% bioavailable following oral administration due to extensive first-pass metabolism. The compound is metabolized by liver enzymes CYP2D6 and CYP2C9 via aromatic ring oxidation and glucuronidation, and then further conjugated by glucuronidation and sulfation. The three active metabolites exhibit only one tenth of the vasodilating effect of the parent compound.
Labetalol is readily absorbed in man after oral administration, but the drug, which is lipid soluble, undergoes considerable hepatic first-pass metabolism and has an absolute bioavailability of approximately 25%. There are no active metabolites, and the elimination half-life of the drug is approximately 6 hours.

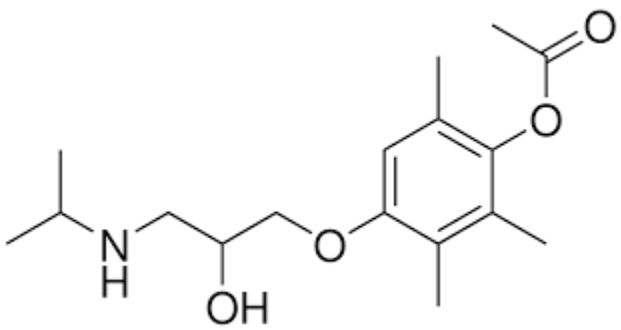
- Therapeutic uses:

They are used in the treatment of hypertension, angina pectoris, cardiac arrhythmia, glaucoma, congestive heart failure. –

- Adverse reactions:

Neurologic Headache, Dizziness
Gastrointestinal: Nausea, Dyspepsia
Cholinergic Nasal congestion
Respiratory: Dyspnea

Metipranolol



- Mechanism of action :

It is known that metipranolol binds the beta 1 and beta 2 adrenergic receptors, the mechanism of metipranolol's action are not known. It has no significant intrinsic sympathomimetic activity, and has only weak local anesthetic (membrane-stabilizing) and myocardial depressant activity. It appears that the ophthalmic beta-adrenergic blocking agents reduce aqueous humor production, as demonstrated by tonography and fluorophotometry. A slight increase in aqueous humor outflow may be an additional mechanism

- Metabolism:

Metipranolol is very rapidly and completely deacetylated in man, so all pharmacokinetic data refer to deacetyl metipranolol.

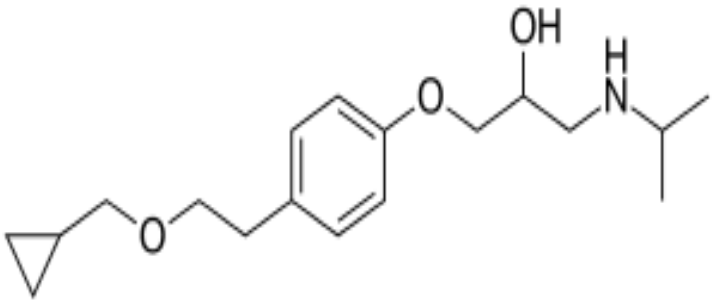
- Therapeutic uses:

Metipranolol is a betal and beta 2 (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. Metipranolol is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. Metipranolol, when applied topically to the eye, has the action of reducing elevated, as well as normal, intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss and optic nerve damage. Metipranolol reduces intraocular pressure with little or no effect on pupil size or accommodation in contrast to the miosis which cholinergic agents are known to produce.

- Adverse Reactions:

Temporary discomfort of the eye, blurred vision, watery eyes, headache, drowsiness, or dizziness may occur. Rare but very serious side effects occur: trouble breathing, chest/jaw/left arm pain, weakness on one side of the body, slurred speech and confusion.

Betaxolol



- Mechanism of action

Betaxolol selectively blocks catecholamine stimulation of beta (1)-adrenergie receptors in the heart and vascular smooth muscle. These results in a reduction of heart rate, cardiac output, systolic and diastolic blood pressure, and possibly reflex orthostatic hypotension. Betaxolol can also competitively block beta (2)-adrenergic responses in the bronchial and vascular smooth muscles, causing bronchospasm.

- Metabolism:

Primarily hepatic. Approximately 15% of the dose administered is excreted as unchanged drug, the remainder being metabolites whose contribution to the clinical effect is negligible.

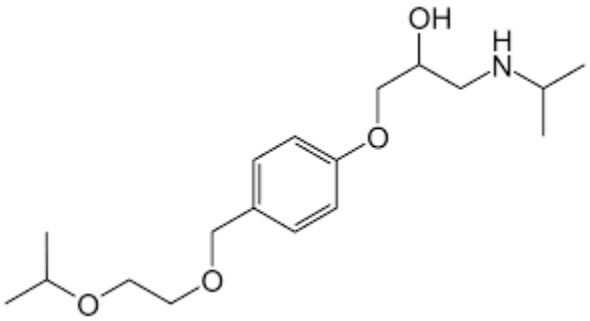
- Therapeutic uses:

This medication is used to treat high blood pressure. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Betaxolol 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 that affect the heart and blood vessels. This results in a lowering of the heart rate and blood pressure.

- Adverse reactions:

Dizziness, light-headedness, drowsiness and headache may occur as your body adjusts to the medication. Trouble sleeping, decreased sexual ability, stomach upset, nausea, diarrhea, sore throat, cold hands and feet, dry eyes, tingling, numbness, and weakness may also occur.

Bisoprolol:



- Mechanism of action

Bisoprolol is cardioprotective because it selectively and competitively blocks catecholamine (adrenalin) stimulation of Beta 1 adrenergic receptors (adrenoreceptors), which are mainly found in the heart muscle cells and heart conduction tissue (cardiospecific), but also found in juxtaglomerular cells in the kidney. Normally, adrenalin and noradrenalin stimulation of the Beta 1 adrenoreceptor activates a signalling cascade (Gs protein and cAMP) which ultimately leads to increased contractility and increased heart rate of the heart muscle and heart pacemaker, respectively Bisoprolol competitively blocks the activation of this cascade, so decreases the adrenergic tone/stimulation of the heart muscle and pacemaker cells. Decreased adrenergic tone shows less contractility of heart muscle and lowered heart rate of pacemakers.

- Metabolism:

Bisoprolol exhibits a high absolute bioavailability (90%) because of its nearly complete absorption (greater than 90%) and small first-pass effect (10%).
Bioavailability is independent of food intake.

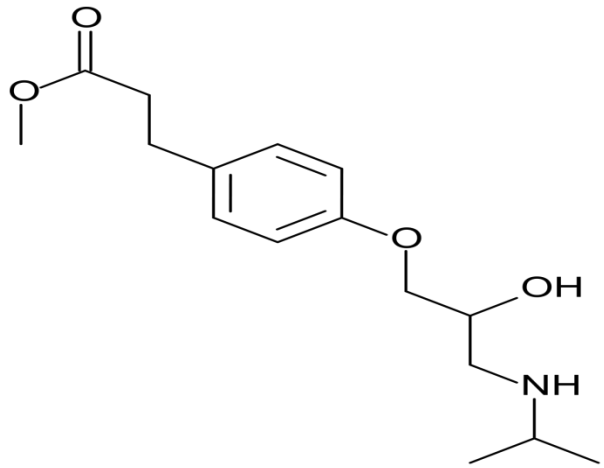
- Therapeutic Uses:

Bisoprolol is beneficial in treatment for high blood pressure (hypertension), reduced blood flow to the heart (cardiac ischemia); congestive heart failure, and preventive treatment before and primary treatment after heart attacks, decreasing the chances of recurrence. Bisoprolol targets hypertension (elevated blood pressure). In cardiac ischemia, the drug is used to reduce the activity of the heart muscle, so reduces oxygen and nutrient demand, and reduced blood supply can still transport sufficient amounts of oxygen and nutrients.

- Adverse Reactions:

Overdose of bisoprolol leads to fatigue, hypotension, low blood sugar, bronchospasms, and bradycardia. Bronchospasms and low blood sugar because at high doses drug can be an antagonist for Beta 2 adrenergic receptors located in lung and in liver. Bronchospasm is due to blockage in lungs of Beta 2 receptor and low blood sugar because of decreased stimulation of glycogenolysis and gluconeogenesis in the liver via Beta 2 receptor.

Esmolol:



- Mechanism of action

Similar to other beta-blockers, esmolol blocks the agonistic effect of the sympathetic neurotransmitters by competing for receptor binding sites. Because it predominantly blocks the beta-1 receptors in cardiac tissue, it is said to be cardioselective. In general, so-called cardioselective beta-blockers are relatively cardioselective; at lower doses they block beta-1 receptors only but begin to block beta-2 receptors as the dose increases.

- Metabolism:

Esmolol is rapidly metabolized by hydrolysis of the ester linkage, chiefly by cytosol of red blood cells and not by plasma cholinesterase or red cell membrane acetylcholinesterase.

- Therapeutic Uses:

To terminate supraventricular tachycardia, episodic atrial fibrillation or flutter, arrhythmia during anaesthesia. To reduce HR and BP during and after cardiac surgery and in early treatment of myocardial infarction.

- Adverse Reactions: Hypotension asymptomatic (25-38%), Hypotension symptomatic (12%), nausea, dizziness, somnolence, agitation, confusion, headache, fatigue, vomiting.