DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM

Objectives

After reading this chapter the students is expected to:

•Correctly identify the different classes of drugs affecting the autonomic nervous system(autonomic drugs)
•Discuss the effects and therapeutic uses of various drugs

•Identify side effects and contraindications of commonly used autonomic drugs.
•Prescribe autonomic drugs in clinical practice rationally.

INTRODUCTION

The nervous system controls all the major functions of the body. It is divided into central and peripheral nervous systems. The peripheral nervous system includes the somatic and autonomic nervous systems which control voluntary and involuntary functions respectively.

The ANS controls the vegetative functions of the body. These include functions like circulation, respiration, digestion and the maintenance of body temperature.

The ANS is subdivided into two major sub-divisions; this classification is based on both anatomic and physiologic grounds; the two subdivisions are sympathetic (thoracolumbar) and parasympathetic (craniosacral). Autonomic nerves are actually composed of two neuron systems, termed preganglionic and postganglionic, based on anatomical location relative to the ganglia. A preganglionic neuron has its cell body in the spinal cord or brain.

The sympathetic nervous system arises from the thoracic and lumbar areas of the spinal cord and the preganglionic fibers for the parasympathetic nervous system arise from the cranial and sacral nerves. The postganglionic neurons send their axons directly to the effector organs (peripheral involuntary visceral organs). Autonomic innervation, irrespective of whether it belongs to the parasympathetic or the sympathetic nervous system, consists of a myelinated preganglionic fiber which forms a synapse with the cell body of a non-myelinated second neuron termed post-

ganglionic fiber. The synapse is defined as a structure formed by the close apposition of a neuron either with another neuron or with effector cells.

In terms of function, the parasympathetic nervous system is concerned primarily with conservation and restoration of function.

In contrast, the sympathetic nervous system is concerned with the expenditure of energy, i.e., it has almost opposite functions with parasympathetic nerve stimulation and it is usually associated with arousal or in emergency situations, i.e., prepares the body for fight-or-flight responses.

To understand autonomic nervous system pharmacology, it is very important to know how the system works and clearly identify the mechanisms behind the functions, i.e., nerve transmission.

There are two important neurotransmitters in the autonomic nervous system. These are acetylcholine and noradrenaline (norepinephrine)

Acetylcholine is a neurotransmitter which is released after stimulation of the parasympathetic nervous system to act on effector organs (cells) to elicit their response, but it also acts as a neurotransmitter:

- At the ganglia of both sympathetic and parasympathetic nervous system,
- At postganlionic sympathetic nerve endings to blood vessels of skeletal muscles and sweat glands(eccrine),
- At the neuromuscular junction of skeletal muscles (somatic motor fibers to skeletal muscle),
- Between some neurons in the CNS, and
- At preganglionic nerve endings to the adrenal medulla.

The process of neurotransmission involves passage of an impulse across a synapse.

Acetylcholine is synthesized inside the cytoplasm of nerve fibers from acetyl coenzyme A and choline through the catalytic action of the enzyme choline acetyltransferase. Once synthesized, it is transported form the cytoplasm into the vesicles to be stored; when action potential reaches the terminal and the latter undergoes stimulation, acetylcholine is released to the synaptic cleft. After release

from the presynaptic terminal the molecule binds to and activates an acetylcholine receptor (cholinergic receptor) located on effector cell. Finally, it is hydrolyzed into choline and acetate by acetyl cholinesterase enzyme and thereby the action of the transmitter is terminated.

Cholinergic receptors are classified into muscarinic and nicotinic cholinergic receptors.

The response of most autonomic effector cells in peripheral visceral organs is typically muscarinic, whereas the responses in parasympathetic and sympathetic ganglia, as well as responses of skeletal muscle are nicotinic.

The effect of parasympathetic nervous system activity in an organ may be produced either by stimulation of a parasympathetic nerve fibers supplying the organ or by the application of acetylcholine or other parasympathomimetics to the effector cells. This is known as ***cholinergic activity.***

Noradrenaline is the neurotransmitter released by post ganglionic sympathetic nerves to elicit its effect on effectors cells. The post-ganglionic sympathetic fibers are called noradrenergic or adrenergic. Sympathetic nerve activity may be demonstrated by sympathetic nerve stimulation or by application of noradrenaline or adrenaline or other sympathomimetics, i.e. '***adrenergic***

activity', except in the case of sweat glands and blood vessels to skeletal muscles where acetylcholine is released as a neurotransmitter.

Adrenergic neuron terminals synthesize noradrenaline, store it in vesicles and release it to effector cells upon stimulation of the nerve. The transmitter is synthesized from precursor tyrosine (amino acid) through several processes which are potential sites of drug action. After release to receptor sites noradrenaline produces its effects. Termination of noradrenergic transmission results from several processes such as reuptake into the nerve terminal (reuptake1), diffusion away from the synaptic cleft and subsequent reuptake into the perisynaptic glia or smooth muscle (reuptake2) or degradation by enzymes. Reuptake into the nerve terminal is the most important mechanism for termination of the effects of noradrenaline.

Receptors that respond to adrenergic nerve transmitter are termed adrenergic receptors. These receptors are subdivided into alpha and beta adrenoreceptor types

on the basis of both agonist and antagonist selectivity. The receptors have subclasses depending on drug selectivity. These are alpha 1 and 2 and beta 1, 2 and 3.

Table 2.1: Distribution of adrenoceptor subtypes and their actions

Type	**Tissue**	**Actions**
Alpha$_1$	Most vascular smooth muscles	Contraction
	Pupillary dilator muscle	Mydriasis
	Heart	Increase force of contraction
Alpha$_2$	Adrenergic nerve terminals	Inhibition of transmitter release
	Platelets	Aggregation
Beta$_1$	Heart	Increased rate and force of contraction
Beta2	Respiratory, uterine, and vascular smooth muscle	Relaxation
	Human liver	Glycogenolysis
Beta$_3$	Fat cells	Lipolysis

There are five key features of neurotransmitter function representing potential targets of pharmacologic therapy. These are synthesis, storage, release, activation of receptors and termination of the action of the transmitter.

Fig 2.3: Proposed site of action of drugs on the synthesis, action, and fate of norepinephrine at sympathetic neuroeffector junctions

AUTONOMIC DRUGS

There are several drugs affecting the autonomic nervous system which, for a better understanding of specific drugs, are classified into groups.

1.Drugs acting on the sympathetic nervous system

a)Sympathomimetics or adrenergic drugs: are drugs that mimic the effects of sympathetic nerve stimulation.

b)Sympatholytics: are drugs that inhibit the activity of sympathetic nerve or that of sympathomimetics.

2.Drugs acting on the parasympathetic nervous system

a)Parasympathomimetics or cholinergic drugs: are drugs which mimic acetylcholine or the effects of parasympathetic nerve stimulation.

b)Parasympatholytics: are drugs that inhibit parasympathetic nervous system activity or that of cholinergic drugs.

CHOLINERGIC DRUGS

Cholinergic drugs are also called parasympathomimetics because their effect mimics the effect of parasympathetic nerve stimulation. Administration of these drugs will result in an increase in the parasympathetic activities in the systems innervated by cholinergic nerves.

There are two groups of cholinergic drugs:

1.*Direct-acting*: bind to and activate muscarinic or nicotinic receptors (mostly both) and include the following subgroups:
a.Esters of choline: methacholine, carbachol, betanechol

b.Cholinergic alkaloids: pilocarpine, muscarine, arecoline, nicotine

2.*Indirect-acting*: inhibit the action of acetylcholinesterase enzyme

a.Reversible: neostigmine, physostigmine, edrophonium

b.Irreversible: Organophosphate compounds; echothiophate

The actions of acetylcholine may be divided into two main groups: -

1.Nicotinic actions- those produced by stimulation of all autonomic ganglia and the neuromuscular junction
2.Muscarinic actions- those produced at postganglionic cholinergic nerve endings

ESTERS OF CHOLINE

ACETYLCHOLINE is the prototypical cholinergic agent. It functions as a neurotransmitter at all cholinergic sites in the body; because of its unique pharmacokinetic properties, it has never been used in medical therapeutics; the discussion which follows is for academic exercise.

Pharmacokinetics

Acetylcholine is poorly absorbed from the gastric mucosa; therefore it is ineffective if given orally. The recommended way of administration is parenteral. In the blood it is rapidly hydrolyzed by the enzyme cholinesterase into acetic acid and choline; this makes its duration of action very short and unreliable for therapeutic purposes.

Pharmacodynamics

As mentioned earlier it has two types of actions: nicotinic and muscarinic; the muscarinic actions are of main interest and are discussed below.

ƒ Cardiovascular system HeartÆ slow heart rate

Blood vessels↱·vasodilator

Blood pressure↱·falls because of the effect on the heart and blood revels

i) Gastrointestinal tract

It stimulates the tone and motility of the GI tract but the sphincters will be relaxed

ii) Urinary tract

It stimulates the detrusor muscle and relaxes the internal urethral sphincter resulting in evacuation of bladder

iii) Bronchioles

It increase bronchial secretion and brings about bronchoconstriction

iv)*Eye*- It has two effects- miosis and accommodation for near objects because of stimulation of the constrictor pupillae and ciliary muscles respectively.

v)*Exocrine glands*- it stimulates salivary, gastric, bronchial, lachrymal and sweat gland secretions.

SYNTHETIC CHOLINE ESTERS. These are synthetic derivatives of choline and include metacholine, carbachol and betanechol. These drugs have the following advantages over acetylcholine:

•They have longer duration of action,

•They are effective orally as well as parenterally, and

•They are relatively more selective in their actions.

CARBACHOL

Pharmacokinetics

It is completely absorbed from the gastro intestinal tract and is stable towards hydrolysis by cholinesterase enzyme; therefore it can be given both orally and parenteraly with almost similar dosage.

Pharmacodynamics

It has similar actions to those of acetylcholine with pronounced effects on the gastro intestinal tract and the urinary bladder

Indications

•Glaucoma

•Retention of urine (postoperative)

•Paralytic ileus

BETANECHOL

This drug is similar to carbachol in all parameters, i.e., pharmacokinetics, pharmacodynamics and clinical indications; it has a better advantage over carbachol because it has fewer side effects as a result as lack of nicotinic actions.

Contra indications to the use of choline esters

1.Bronchial asthma because they may induce bronchial constriction and increase bronchial secretions

2.Hyperthyroidism because of the danger of inducing atrial fibrillation

3. Peptic ulcer disease because of the increase in gastric acid secretion

4.Coronary insufficiency because the hypertension produced will further compromise coronary blood flow

5.Mechanical intestinal and urinary outlet obstruction

CHOLINERGIC ALKALOIDS

1.Those with chiefly nicotinic actions include nicotine, lobeline etc.

2.Those with chiefly muscarinic actions include muscarine, pilocarpine, etc.

PILOCARPINE

Pharmacokinetics

This drug is readily absorbed from the gastrointestinal tract and it is not hydrolyzed by cholinesterase enzyme. It is excreted partly destroyed and partly unchanged in the urine.

Pharmacodynamics

The drug directly stimulates the muscarinic receptors to bring about all the muscarinic effects of acetylcholine.

Indications

•Glaucoma

ANTICHOLINESTERASE DRUGS

The commonly used cholinesterase inhibitors fall into three chemical groups:

1.Simple alcohols bearing quaternary amines, e.g., edrophonium

2.Carbamate and related quaternary or tertiary amines, e.g., neostigmine, physostigmine

3.Organic derivatives of phosphates, e.g., isofluorophate, echothiophate

PHYSOSTIGMINE

Pharmacokinetics

This drug is completely absorbed from the gastrointestinal and is highly distributed throughout the body; it can pass the blood brain barrier.

Pharmacodynamics

Inhibits the enzyme cholinesterase; therefore, it increases and prolongs the effect of endogenous acetylcholine at the different sites.It has no direct effect on cholinergic receptors.

Indications

•Glaucoma

•Atropine over dosage

NEOSTIGMINE

Pharmacokinetics

This drug is poorly absorbed from the gastro intestinal tract and is poorly distributed throughout the body; it cannot pass the blood brain barrier.

Pharmacodynamics

Just like physostigmine, it inhibits cholinesterase enzyme; but unlike physostigmine, it has a direct nicotinic action on skeletal muscles.

Indications

•Myasthenia gravis

•Paralytic Ileus

•Reversal of effect of muscle relaxants, e.g. tubocurarine

•Post operative urine retention

Organophosphates such as echothiophate, isofluorophate, etc. combine with cholinesterase irreversibly and thus hydrolysis is very slow.

They may be used in glaucoma. Other organophosphates like parathion and malathion are used as insecticides. Poisoning with organophosphates is an important cause of morbidity and mortality all over the world. It usually results from:

•Occupational exposure as in persons engaged in spraying insecticides,

•Accidental exposure, and

•Ingestion of any of these compounds with suicidal intent.

ANTICHOLINERGICS

Anticholinergics block the effects of acetylcholine and other cholinergic drugs at cholinergic receptors of effector cells. Anticholinergics fall into two major families:

1.Antinicotinics which include ganglion blockers such as hexamethonium, trimethaphan, etc., and neuromuscular blockers such as gallamine, tubocurarine, pancuronium, etc.

2.Antimuscarinics include tertiary amines such as atropine, scopolamine, tropicamide, etc, andquaternary amines such as propantheline, ipratropium, benztropine, etc.

ATROPINE

Atropine is found in the plant Atropa belladonna and it is the prototype of muscarinic antagonists.

Pharmacokinetics

Atropine is absorbed completely from all sites of administration except from the skin wall, where absorption is for limited extent; it has good distribution. About 60% of the drug is excreted unchanged in urine.

Pharmacodynamics

Atropine antagonizes the effect of acetylcholine by competing for the muscarinic receptors peripherally and in the CNS; therefore the effects of atropine are opposite to the acetylcholine effects.

Organ-system Effects:

CNS: - lower doses produce sedation

-higher doses produce excitation, agitation and hallucination *Eyes:* - relaxation of constrictor pupillae (mydriasis)

-relaxation or weakening of ciliary muscle (cycloplegia-loss of the ability to accommodate)

CVS: - blocks vagal parasympathetic stimulation (tachycardia) - vasoconstriction

Respiratory: - bronchodilatation and reduction of secretion

GIT: - decreased motility and secretions

GUS: - Relaxes smooth muscle of ureter and bladder wall; voiding is slowed.

Sweat Glands: - suppresses sweating

Clinical Indications

Pre anesthetic medication -to reduce the amount of secretion and to prevent excessive vagal tone due to anesthesia.

As antispasmodic in cases of intestinal, biliary, and renal colic

Heart block

Hyperhidrosis

Organophosphate poisonings

Side effects

•Dryness of the mouth, tachycardia and blurred vision

•Retention of urine

Contraindications

Glaucoma

Bladder outlet obstruction.

HYOSCINE (SCOPOLAMINE)

This drug has the same effect as atropine except for some differences which includes:-

-It has shorter duration of action

-It is more depressant to the CNS.

-All other properties are similar to atropine. It has certain advantage over atropine. These include:

3.Better for preanesthetic medication because of strong antisecretory and antiemetic action and also brings about amnesia

4.Can be used for short- travel motion sickness

SYNTHETIC ATROPINE DERIVATIVES

There are a number of synthetic atropine derivatives, which are used in the treatment of various conditions, their actions are similar to that of atropine but have fewer side effects. These groups of drugs include

1.Mydriatic atropine substitutes, this group of drugs have shorter duration of action than atropine and are used locally in the eye; drugs included: Homatropine, Eucatropine etc.

2.Antiseccretory antispasmodic atropine substitutes:

- Effective more localized to the GI. Drugs include: propantheline and hyoscine

3.Antiparkinsonian atropine substitute: - drugs like Benztropine, Trihexyphenidyl

4.Atropine substitutes which decrease urinary bladder activity like oxybutynin

5.Atropine substitutes used in bronchial asthma drugs like ipratropium

ADRENERGIC DRUGS

As their name suggests, these drugs resemble sympathetic nerve stimulation in their effects; they may be divided into two groups on the basics of their chemical structure.

1**. Catecholamines**: -these are compounds which have the catechol nucleus.

Catecholamines have a direct action on sympathetic effectors cells through interactions with receptor sites on the cell membrane.

The group includes adrenaline, noradrenaline, dopamine, isoprenaline, and dobutamine.

-*Noncatecholmines:* - lack the catechol nucleus.

They may directly act on the receptors or may indirectly release the physiologic catecholamines- e.g. ephedrine, phenylephrine, amphetamine

Adrenergic drugs, like cholinergic drugs, can be grouped by mode of action and by the spectrum of receptors that they affect.

a.*Direct mode of action:* directly interact with and activate adrenoreceptors, e.g., adrenaline and noradrenaline

b.*Indirect mode of action:* their actions are dependent on the release of endogenous catecholamines. This may be

i.Displacement of stored catecholamies from the adrenergic nerve endings, e.g., amphetamine, tyramine

ii.Inhibition of reuptake of catecholamines already released, e.g. cocaine, tricyclic antidepressants

Both types of sympathomimetics, direct and indirect, ultimately cause activation of adrenoreceptors leading to some or all characteristic effects of the catecholamines.

Organ-system Effects of Activation of the Adrenergic System

1.CVS:

a.*Heart:* increased rate and force of contraction, increased cardiac output, myocardial demand, and AV conduction

b.*Blood Vessels and Blood pressure*: constriction of blood vessels in the skin and mucous membranes

-Dilatation of skeletal muscle vessels

-Adrenaline increases systolic and decreases diastolic blood pressure at low doses but increases both at higher doses
-Noradrenaline increases both systolic and diastolic blood pressure

2.Smooth Muscle:

a.Bronchi: relaxation.

b.Uterus: relaxation of the pregnant uterus

c.GIT: relaxation of wall muscles and contraction of sphincters

d.Bladder: relaxation of detrusor muscle; contraction of sphincter and trigone muscle

3.*Eye:* mydriasis; reduction of intraocular pressure in normal and glacucomatous eyes

4.*Respiration:* Bronchodilatation; relief of congestion; mild stimulation of respiration

5.*Metabolic:* Increased hepatic glycogenolysis; decreased peripheral glucose intake; increased free fatty acids in the blood (lipolysis)
6.*CNS:* excitement, vomting, restlessness

7.*Skeletal muscle*: facilitation of neuromuscular transmission and vasodilatation

Drugs Acting on the Adrenergic Receptor Subtypes

	α_1	α_2
Agonist	Phenylephrine Methoxamine	Clonidine Oxymetazoline
Antagonist	Prazosin Phentolamine Phenoxybenzamine	Yohimbine Phentolamine Phenoxybenzamine

β_1

Dobutamine

Isoproterenol

Terbutaline

Propranolol

Pindolol

Atenolol

Metoprolol

Timolol

β_2

Salbutamol

Terbutaline

Isoetharine

Propranolol

Pindolol

Butoxamine

Timolol

Adrenaline stimulates all the four receptor subtypes.

Noradrenaline stimulates both alpha receptors and beta$_1$ but has very poor affinity for beta$_2$ receptors. Labetalol blocks all beta receptors as well as some alpha receptors.

ADRENALINE

This is the prototype of adrenergic drugs and is produced in the body by the cells of the Adrenal medulla and by chromaffin tissues.

Pharmacokinetics

Adrenaline is rapidly destroyed in the gastrointestinal tract, conjugated, and oxidized in the liver. It is therefore ineffective when given orally and should be given intramuscularly or subcutaneous. Intravenous injection is highly dangerous and is likely to precipitate ventricular fibrillation. The drug may how ever, be given by nebulizer for inhalation when its relaxing effect on the bronchi is desired or it may be applied topically to mucus membranes to produce vasoconstriction. Because of the extensive metabolism of the drug in liver, little is excreted unchanged in the urine.

Pharmacodynamics

Adrenaline directly stimulates all the adrenergic receptors both and brings about effects of sympathetic nerve stimulation. Its action may be divided in to two, depending on the type of receptor stimulated.

The α effects consist of vasoconstriction in skin and viscera, mydriasis, platelet aggregation and some increase in blood glucose. The ß effects consists of increased contractility and rate of heart with a decreased refractory period (ß1), vasodilatation in

muscles and coronary vessels (ß2), bronchial relaxation (ß2) uterine relaxation (ß2), hyperglycemia, lactic acidemia and increased circulating free fatty acids.

Indications

1.Acute bronchial asthma

2.Anaphylaxis

3.Local haemostatic to stop bleeding in epistaxis

4.With local anesthesia to prolong the action

5.Cardiac arrest

Adverse reactions

1.Anxiety, restlessness, headache tremor

2.Anginal pain

3.Cardiac arrhythmias and palpitations

4.Sharp rise in blood pressure

5.Sever vasoconstriction resulting in gangrene of extremities

6.Tearing, conjunctival hyperemia

Contra indications

1.Coronary diseases

2.Hyperthyroidism

3.Hypertension

4.Digitalis therapy

5.Injection around end arteries

NOR ADRENALINE

Nor adrenaline is the neurochemical mediator released by nerve impulses and various drugs from the postganglionic adrenergic nerves. It also constitutes 20% of the adrenal medulla catecholamine out put.

Pharmacokinetics

Like adrenaline, noradrenaline is ineffective orally so it has to be given intravenously with caution. It is not given subcutaneous or intramuscularly because of its strong

vasoconstrictor effect producing necrosis and sloughing. The metabolism is similar to adrenaline; only a little is excreted unchanged in urine.

Pharmacodynamics

Nor adrenaline is a predominantly α receptor agonist with relatively less β agonist action when compared to adrenaline.

Indication

Nor adrenalines is used as hypertensive agent in hypotensive states

E.g. During spinal anesthesia or after sympathectomy.

Adverse effects include:

-Anxiety, headache, bradycardia are common side effects

-Severe Hypertension in sensitive individuals

-Extravasation of the drug causes necrosis and sloughing.

ISOPRENALINE DOPAMINE, DOBUTAMINE. These are the other catecholamines which have similar properties to adrenaline and noradrenaline.

Dopamine is naturally occurring and is a precursor of noradrenaline. The other two- isoprenaline and dobutamine- are synthetic. These drugs have advantage over the others because they are

more selective in their action so that they have fewer side effects than adrenaline and nor adrenaline. Dopamine and dobutamine are very useful drugs for the treatment of shock.

NON- CATECHOLAMINES

Most of the non- catecholamines function by releasing the physiologic catecholamines from the postganglionic nerve endings

EPHEDRINE

Pharmacokinetics

Ephedrine in absorbed from the gastrointestinal tract and from all parenteral sites. It has a good distribution through out the body and is resistant to hydrolysis by the liver

enzymes. Major proportion of the drug is excreted unchanged in the urine. Because of its stability to metabolism it has long duration of action than the catecholamines.

Pharmacodynamics

Ephedrine stimulates both α and β receptors. This effect is partly by a direct action on the receptors and partly indirectly by releasing noradrenaline from its tissue stores the effect of the drug to various organs and systems is similar to that of adrenaline. It is also a mild CNS stimulant.

Indications:

1.Bronchial asthma: - usually as a prophylactic for prevention of attacks
2.Nasal decongestion
3.Mydriasis
4.Heart block
5.Nocturnal enuresis

Side effects

The side effects are similar to those of adrenaline; but in addition it may produce insomnia and retention of urine.

Contraindications

They are the same as Adrenaline.

Based on their selectivity to specific receptors the rest of the catecholamines, are classified but it is very difficult to exhaust all the drugs. More over their effect and pharmacology is discussed where they are clinically indicated.

ADRENERGIC BLOCKERS

Adrenergic receptor blockers may be considered in two groups:

1.Drugs blocking the ą adrenergic receptor
2.Drugs blocking theβ Adrenergic receptor

These drugs prevent the response of effectors organs to adrenaline, noradrenaline and other sympathomimetic amines whether released in the body or injected. Circulating catecholamines are antagonized more readily than are the effects of sympathetic nerve stimulation. The drugs act by competing with the catechoamines

for α or β receptors on the effectors organs. They don't alter the production or release of the substances.

α- Adrenergic blockers

Alpha adrenergic receptor antagonists may be reversible or irreversible. Reversible antagonists dissociate from the receptors e.g. phentolamine, tolazoline, prazosin,yohimbine, etc. Irreversible antagonists tightly bind to the receptor so that their effects may persist long after the drug has been cleared from the plasma e.g. phenoxybenzamine

Pharmacologic Effects:

Alpha receptor antagonist drugs lower peripheral vascular resistance and blood pressure. Hence, postural hypotension and reflex tachycardia are common during the use of these drugs. Other minor effects include miosis, nasal stuffiness, etc.

Prazosin

This is an effective drug for the management of hypertension. It has high affinity for $alpha_1$ receptor and relatively low affinity for the $alpha_2$ receptor. Prazosin leads to relaxation of both arterial and venous smooth muscles due to the blockage of $alpha_1$ receptors. Thus, it lowers blood pressure, reduces venous return and cardiac output. It also reduces the tone of internal sphincter of urinary bladder.

Indications:

-Essential hypertension

-Raynaud's syndrome

Benign prostatic hyperplasia

β- ADRENERGIC BLOCKING DRUGS

The β - adrenergic receptor blocking drugs in use may be classified by their selectivity for receptors in different tissues.

1. Drugs blocking all the β receptor effects of adrenaline (non-selective beta blockers) e.g. propanalol, pinadolol, timolol etc

2.Drugs blocking mainly the β1 effects (those on the heart) with less effect on the bronchi and blood vessels (beta1-selective blockers), e.g. atenolol, practalol acebutalol, etc.

PROPRANOLOL

Propranolol is a non- selective β adrenergic blocker; it has also other actions like membrane stabilization.

Pharmacokinetics

Propranolol is almost completely absorbed following oral administration. How ever, the liver, leaving only 1/3 rd of the dose to reach the systemic circulations, metabolizes most of the administered dose. It is bound to plasma to the extent of 90-95%. It is excreted in the urine.

Pharmacodynamics

The drug has the following main actions.

1.Cardiovascular system

•Bradycardia

•Reduces force of contraction

•Reduces blood pressure

2.Respiratory system

•Bronchoconstriction

3.Metabolic system

•Hypoglycemia

4.Central nervous system

•Anti-anxiety action

5.Eye

•Decrease the rate of Aqueous humor production

6.Kidneys:

•Decrease renin secretion

Indications

•Cardiac arrhythmias

•Hypertension

•Prophylaxis against angina

•Myocardial infarction

•Thyrotoxicosis

•Anxiety states (suppression of the physical manifestations of situational anxiety)

•Prophylaxis against migraine attacks

•Glaucoma

Adverse reactions

•GI disturbances like nausea, vomiting

•Heart failure

•Heart block

•Hypotension and severe bradycardia

•Bronchospasm

•Allergic reaction

•Vivid dreams night mare and hallucinations

•Cold hands

•Withdrawal symptoms in case of abrupt discontinuation

•Masking of hypoglycemia in diabetic patients

Contraindications and Precautions:

•Bronchial asthma

•Diabetes mellitus

•Heart failure

•Peripheral vascular disease