Department of Medical Pharmacology, Faculty of Medicine, South Valley University

Pharmacology

for

Fourth Year Physical Therapy Students

by:

Prof. Dr. Al Shaimaa Meky Basry Hasan

Assistant Professor and Head of Medical Pharmacology Department, Faculty of Medicine, South Valley University

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Prof. Dr. Al Shaimaa Meky Basry Hasan

Assistant Professor and Head of Department,
Department of Medical Pharmacology, Qena Faculty of Medicine,
South Valley University, Egypt.

Postdoctoral Fellow, National Institute of Infectious Diseases
(NIID), Toyama 1-23-1, Shinjuku, Tokyo 162-8640, Japan.

Visiting Research Fellow, Department of Stem Cell Biology,
Nagasaki University Graduate School of Biomedical Sciences,
1-12-4 Sakamoto, Nagasaki 852-8523, Japan.

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Contents

General Pharmacology

Pharmacokinetics:
The actions of the body on the drug. What the body does to the drug?
It includes: Absorption, Distribution, Metabolism and Elimination (Excretion).

Absorption of drugs

Definition:
It is the transfer of the drug from its site of administration to the systemic circulation.

Factors affecting drug absorption:
1. Blood flow to absorption site: the highly blood supply to the absorbing area, the better absorption; e.g. intestine.
2. Surface area available for absorption: the larger surface area exposed to the drug, the better absorption; e.g. intestine.
3. Food: it may increase or decrease absorption of drugs; e.g.milk impairs absorption of tetracyclines by forming insoluble compounds.
4. Gut motility: decreased gastric motility as cause by some drugs such as atropine, delays the rate of absorption. While, increased gastrointestinal motility as in severe diarrhea may reduce both the rate and extent of drug absorption since the contact time of the drug with the absorption surface becomes very short.
5. First pass metabolism: metabolism of the drug in the liver or in the gut wall before it reaches the systemic circulation.
6. Solubility of the drug: high lipid soluble drugs cross the membranes better than low lipid soluble.

First-pass metabolism

Some drugs absorbed orally are initially transported to the liver via the portal circulation and metabolized before reaching the systemic circulation. The greater the first-pass effect, the less the drug will reach the systemic circulation when the drug is administered orally.

Gut first-pass effect:
Some penicillins are destroyed by gastric acidity and are known as acid sensitive penicillins, e.g. benzyl penicillin (penicillin G). Also, polypeptide hormones as insulin are destroyed by digestive enzymes.

Hepatic first pass effect (much more important than gut first pass): Some of drugs are largely metabolized by first pass hepatic effect, e.g. propranolol. Other drugs are extensively metabolized, as nitroglycerin, or almost completely metabolized as lidocaine and natural sex hormones. Some drugs as Atenolol and Nadolol are minimally metabolized by the liver.

How to avoid first pass effect?

Increase the dose of orally administered drugs as propranolol and nitroglycerin.

Change the route of administration: the drug may be given I.V. as lidocaine, S.C. as insulin, or sublingual as nitroglycerin.

Drug Distribution

Definition:

It is the transport of the drug from the blood to the site of action. Once the drug is absorbed from any site, i.e. it reaches the systemic circulation; it may be distributed to the body fluids and tissues.

Binding of drugs to plasma proteins:

After reaching the systemic circulation, any drug will be found in 2 forms; the free (unbound) form and the bound form.

Free form:

Diffusible, active, liable to liver metabolism and liable to renal excretion (mostly by glomerular filtration).

Bound Form:

Non-diffusible, inactive, not liable to liver metabolism and not liable to renal excretion.

Drugs are bound reversibly mainly to albumin and to a lesser extent to globulin and αacid glycoprotein.

Some drugs as aspirin and sulphonamides have a highly affinity (are highly bound) to plasma proteins and they displace other drugs with lower affinity as digoxin and warfarin (oral anticoagulant) if administered together, which results in increase in the free "active" form of the latter drugs and this may lead to **severe adverse (toxic) effects:**

- Aspirin and sulphonamides displace digoxin leading to digitalis toxicity.
- Aspirin and sulphonamides displace warfarin leading to bleeding.
- Sulphonamides displace bilirubin from plasma proteins, which increases free bilirubin causing hyperbilirubinemia and may be kernicterus in neonates.

- In conditions causing hypoalbuminemia as in old age, liver diseases, malnutrition or starvation; the free form of drugs as phenytoin (antiepileptic) is higher than in normal individuals and toxic effects may occur with therapeutic doses.

Factors Affecting Drug Distribution:

1. Lipid solubility: high lipid soluble drugs will distribute more readily to tissues than low lipid soluble drugs.
2. Regional blood flow: organs with high blood supply such as heart, kidney and liver accumulate drugs to higher extent than poorly perfused organs such as skin, fat and bone.

3. Binding to plasma proteins: drugs are mainly bound to albumin. Only the free fraction of the drug; unbound form can be distributed, metabolized and eliminated. Binding is nonselective and competitive; drug interactions may occur, e.g. toxicity of warfarin when displaced with aspirin.
4. Capillary permeability: many drugs do not readily distribute into the brain in comparison with other tissues e.g. liver and spleen due to the presence of blood brain barrier which have a unique capillary structure (brain capillary endothelial cells have continuous tight junctions).

Redistribution of drugs:

Termination of drug effect, when a highly lipid soluble drug that acts on the brain or CVS is given rapidly by IV injection because of its redistribution into other tissues such as muscle and fat.

Some drugs after exerting their effect at their target organs redistribute into other tissues and stay there in their active form till their metabolism and elimination.

For example:

The ultra-short acting anesthetic drug, thiopental.

Drug Biotransformation (Drug Metabolism)

Definition:

These are chemical reactions that occur mainly in **the liver**.

The aim of the drug metabolism is to convert lipid-soluble (lipophilic) drugs into **water soluble** (inactive), more hydrophilic (polar) metabolites readily excreted by the kidneys.

What about water-soluble drugs?

Water-soluble drugs do not undergo metabolism and are excreted unchanged in urine.

Sites of Biotransformation:

- It is enzymatic in nature.
- Liver: enzyme systems involved in drug metabolism are localized mainly in the liver (liver microsomal enzymes; cytochrome P 450 (CYP450).
- Plasma: plasma cholinesterase (pseudocholinestrase) which is responsible for metabolism of some drugs sush as succinylcholine.
- Other organs with significant metabolic capacity are GIT, kidneys and lungs.

Modification of drug activity:

- Liver microsomal enzymes usually transform an active drug to an inactive metabolite (drug detoxification).
- In some cases, an active drug is transformed into another active metabolite (Maintenance of activity).

- In other cases, an inactive compound (prodrug) is transformed into an active metabolite or an active compound is transformed into a toxic metabolite (Drug biotoxification).

Phases of Biotransformation Reactions:

a) Phase I Reactions:

These are **Non-Synthetic** reactions. The drug undergoes; oxidation, reduction, or hydrolysis.

For example:

Hydrolysis of Acetylcholine ⟶ choline + acetic acid

b) Phase II Reactions:

These are **Synthetic** or **Conjugation** reactions. The drug or a metabolite resulting from phase I reaction is "conjugated" with an endogenous polar compound as glucuronic acid, sulphate, glycine, acetate, glutathione or methyl group (i.e. glucoronidation, sulphation, acetylation, and methylation).

Phase II reactions mostly result in drug inactivation, with some exceptions as morphine (active) which is partially converted into morphine 6-glucuronide (active metabolite).

Most drugs are metabolized by phase I reactions followed by phase II reactions, undergo phase I reaction only, or phase II reactions only. Few drugs as isoniazid is metabolized by conjugation (phase II) followed by hydrolysis (phase I), i.e. there is reversal of order of the phases.

Factors affecting Drug Metabolism:

1. Genetic Variation
2. Enzymatic Induction and Inhibition
3. Disease Factors.
4. Age and sex.

1. Genetic Variation:

✓ Genetic variation **(polymorphism)** of the metabolizing enzymes can result in absence (deletion), weak expression or marked expression of the enzyme. Also, it can affect the enzyme activity which leads to wide variability in the response to drugs between individuals.

✓ Consequences of such variation may be therapeutic failure or toxicity, e.g. **Isoniazid**. In some individuals Isoniazid metabolism occurs so rapidly and extensively **(fast or extensive metabolizers)**, resulting in reduced drug efficacy and therapeutic failure in these individuals. While, in others, metabolism of the same drug may be slow and weak **(slow or poor metabolizers)**, resulting in drug toxicity with the usual dose.

- ✓ In addition, genetic abnormalities may result in defective or abnormal enzymes; e.g. genetic defect in pseudocholinesterase enzyme greatly reduces metabolism and increases the action of succinylcholine (skeletal muscle relaxant) and may lead to apnea. This abnormal drug response due to genetic defect is known as **idiosyncrasy**.

2. Enzymatic Induction and Inhibition:

Some drugs increase the activity of hepatic microsomal enzymes (HME) and are known as HME inducers or activators, whereas other drugs reduce or inhibit the activity of HME and are thus called HME inhibitors.

a. Microsomal Enzyme Induction:

Enzyme induction is the process by which exposure to certain drugs results in increase in the activity of liver microsomal enzymes which leads to increase the rate of metabolism of the same drug or another drug producing decrease in drug plasma concentration and therapeutic failure.

Consequences of enzyme induction:

- Increased rate of metabolism of the same drug (auto-induction) or another drugs.
- Decrease in drug plasma concentration resulting in therapeutic failure.
- Decrease the duration of action.
- Enhanced oral first pass metabolism
- Reduced bioavailability.
- If metabolite is active or reactive, increased drug effects or toxicity.

Examples of drug inducers:

Phenobarbital, carbamazepine, phenytoin, androgens, rifampicin, some insecticides as DDT, tobacco smoke and some food preservatives and dyes.

b. Microsomal Enzyme Inhibition:

Enzyme inhibition is the process by which exposure to certain drugs results in decrease in the activity of liver microsomal enzymes which leads to decrease the rate of metabolism of the same drug or another drug producing increase in drug plasma concentration, prolonged pharmacological effects and Increased drug toxicity.

Consequences of enzyme inhibition:

- Decrease in rate of metabolism.
- Increase in the plasma concentration of the drug.
- Exaggerated and prolonged pharmacological effects of the same drug or another drug.
- Increased drug toxicity.

Examples of drug inhibitors:

Cimetidine, Ketoconazol, valproic acid, grape fruit and starvation.

3. Disease Factors:

Liver diseases such as liver cirrhosis markedly decrease the activity of liver microsomal enzymes and the dose of drugs metabolized by these enzymes should be adjusted according to liver function tests.

4. Age and sex:

Newborns, infants and old age metabolize drugs at a rate generally slower than adults. So, they should be treated with lower doses than adults.

For example:

- Chloramphenicol in infants can cause toxic effects in the form of **gray baby syndrome**; the baby becomes cyanosed, hypothermic, flaccid and grey in color. Shock and death may occur.

- In elderly; very old more than 65 years, nifedipine can cause severe hypotension.

- Male sex hormones (androgens) act as liver microsomal enzymes inducers whereas female sex hormones (estrogen and progesterone) act as liver microsomal enzymes inhibitors. This is an important cause why females receive lower doses than males (of the same age and weight).

Excretion

Primary site of drug elimination is the kidneys.
Several other sites exist; lungs (inhalation anaesthetics), bile, milk, little excreted in faeces (streptomycin given orally) unless diarrhea, saliva (morphine), tears and hair (mercury).

Pharmacodynamics

Definition:

Pharmacodynamics studies the effects of the drug on the body.
It includes: The drug effects (therapeutic effects and Side effects / toxic effects) and the mechanism of these effects.

Mechanism of drug actions:

The drugs may act through:

1. Receptor mediated mechanism.
2. Non-receptor mediated mechanism.

1- Receptor mediated mechanism:

Receptor:

Receptor is a protein macromolecular component of a cell with which an endogenous substance or a drug interacts to produce a response. It may be present on the cell membrane (e.g. adrenoceptors & cholinoceptors) or inside the cell (e.g. steroid receptors).
Binding of the drug with its receptor results in the formation of drug receptor complex (DR) which is responsible for triggering the biological response.

The receptor has two functions:

a. Ligand (drug) binding.
b. Message propagation (signaling) to produce the intended response in the target cell.

Therefore, it is suggested that within the receptor there are ligand binding domain and effector domain.

Ligand binding: Ligands are molecules (e.g. drug molecules) that attach selectively to a particular receptor. The interaction of the drug with the receptor is analogous to **lock and key** where the drug would fit properly into the receptor and activate it.

Following this binding, the receptor exerts its regulatory actions directly on intermediate cellular molecules called **transducers**.
The transducers may be an enzyme e.g. adenyl cyclase, or transport proteins that create, move or activate intracellular **second messengers** e.g. cAMP, inositol triphosphate or ions like Ca^{++}.

The second messengers can diffuse inside the cell and transmit information to a variety of cellular targets.

2- Non-receptor mediated mechanisms:

1- Physicochemical: e.g. purgatives and osmotic diuretics which owe their action to osmotic effect.

2- Chemical: Neutralization, e.g. antacids neutralize the gastric acidity to treat peptic ulcer.

3- Enzymes: Physostigmine reversibly inhibits cholinesterase enzyme.

Types Of drug receptors:

1. Ion-channels receptors
2. G-protein-coupled receptors
3. Receptors linked to tyrosine kinase
4. Intracellular (cytoplasm or nucleus) receptors

1- Ionotropic receptors (ligand-gated ion channel receptors):
The receptor is linked directly to ion channels in plasma membrane so that when a drug (ligand) binds to the receptor, an ion channel is opened for ionic transport.

Examples:

- Nicotinic cholinergic receptors. When acetylcholine neurotransmitter (as a ligand) binds to nicotinic receptors, ionic sodium channels are opened and sodium transports into the cell.

- These receptors are concerned usually with fast synaptic transmission.

2- G-protein coupled receptors (GPCR):

- G-protein coupled receptors are large membrane bound proteins with an extracellular amino terminus and several loops that comprise the ligand binding site & a carboxy terminus that protrudes into the cytoplasm where a binding site for a G-protein (guanine nucleotide binding protein) is located.

- When a drug binds to GPCR, these binding triggers activation of the G-protein with consequent increase of the activity of effectors (transducers) like adenylcyclase, & phospholipase enzymes.

- The transducers in turn change the concentration of intracellular second messengers such as cAMP, cGMP, inositol triphosphate (IP3) or Ca++. This is called **Signaling Mechanism**.

Examples of GPCR are the muscarinic cholinergic, adrenergic, dopaminergic, serotonin and opiates receptors.

3. Receptors linked to tyrosine kinase:

- ✓ These are transmembrane receptors that have two domains; an extracellular domain for drug binding and a cytoplasmic domain with enzymatic activity e.g. tyrosine kinase enzyme.

- ✓ Binding of the drug to the extracellular domain stimulates the activity of tyrosine kinase enzyme in the cytoplasm leading to phosphorylation of target proteins at its tyrosine residue. This creates an intracellular signal that can be maintained even after the ligand has been dissociated from the binding site. This is called **hit and run mechanism**.

- ✓ ***Example*** of this mechanism is insulin and growth factors receptors.

4. Intracellular receptors:

- These receptors are not associated with plasma membrane and are located intracellular.

- The receptors are usually stimulated by ligands which are lipid soluble and can cross the cell membrane e.g. steroid hormones, thyroid hormone and vitamin D.

Drug-receptor interaction:

1. Agonists:

Drugs that bind to the receptor and initiate its function. The drug binds to a receptor and activates the receptor to produce a biological response.
The drug binds to its specific receptors and produces an action similar to the action produced by an endogenous regulatory substance already present in the body e.g. hormones or neurotransmitters.
Agonist has both affinity and intrinsic activity towards the receptor.

Examples of agonists: Acetylcholine and Adrenaline.

- ❖ **Affinity:** the tendency of a drug to bind to a receptor.
- ❖ **Efficacy or intrinsic activity:** the ability of a drug-receptor complex to produce a pharmacological response is called efficacy or intrinsic activity. If a full agonist has an intrinsic activity = 1, that of pure antagonist is = 0 and that of a partial agonist is between 0 and1.

2. Antagonists:

Drug that blocks the biological response by binding to and blocking the receptors thus reducing or preventing the action of the agonist.
Drug binds to the receptors without producing a response and by occupying the receptors they prevent action of agonists.
Antagonist has affinity to the receptor but lacks intrinsic activity.

Example of antagonists: Prazosin in treatment of hypertension by blocking action of endogenous catecholamines on alpha adrenergic receptors by occupation of these receptors.

Drug antagonism:

1. Physiological antagonism
2. Chemical antagonism
3. Pharmacological antagonism

1. Physiological antagonism:

When a drug produces an effect opposite to the physiological effect of an agonist by acting on different receptors, it is called a physiological antagonist.

Example is epinephrine which increases blood pressure in anaphylactic shock caused by histamine release.

Epinephrine acts on α-adrenergic receptors causing vasoconstriction while histamine produces vasodilatation by action on histamine receptors.

2. Chemical antagonism:

It occurs when two substances chemically interact to neutralize the action of each other.

Example is protamine sulphate (positively charged) is an antidote to heparin (negatively charged anticoagulant).

3. Pharmacological antagonism:

1- Competitive Antagonists:

They compete with agonist for the same receptor site. They bind reversibly to the receptor.

Increasing the agonist concentration can displace the antagonist i.e. shift to the right (rightward shift) in the dose response curve.

Examples: Atropine can reversibly antagonize the action of Acetylcholine.

2- Noncompetitive Antagonist(Irreversible Antagonists):

Noncompetitive antagonist binds irreversibly to the receptor (e.g. by covalent bond), antagonist can not be displaced by excess agonist.

Increase of the concentration of the agonist in the presence of non-competitive antagonist results in a decrease in the maximal effect (i.e. downward shift) of the dose response curve.

Examples: Phenoxybenzamine can irreversibly antagonize the action of Adrenaline.

Types of drug actions

1. Desired: therapeutic action.
2. Undesired: adverse drug reactions.

Adverse drug reactions:

a. Side effects.
b. Toxic effects.
c. Allergic reactions.
d. Idiosyncrasy.

a. Side effects:

Unwanted effects resulting from therapeutic doses, e.g. drowsiness caused by antihistamines.

b. Toxic effects:

Unwanted effects resulting from high doses, usually dose related, e.g. sever hypotension by antihypertensive drugs.

c. Allergic reactions (Hypersensitivity):

It is an abnormal unpredictable and dose independent reactions which occur following the administration of certain drug in sensitive patients, e.g. anaphylactic shock caused by Penicillin.

d. Idiosyncrasy:

It is an abnormal unpredictable and dose independent reactions due to genetic defects e.g. Succinylcholine apnea in patients with pseudocholinestrase enzyme deficiency.

Drug interactions

Definition:

Concomitant administration of two or more drugs may result in change in the response of one or both drugs.
Interactions can occur by pharmacokinetic or pharmacodynamic mechanisms.

Types of drug-drug interactions:

1- Pharmacodynamic interactions.
2- Pharmacokinetic interactions.

1- Pharmacodynamic interactions:

In pharmacodynamic interactions, the effects of one drug are changed by the 2nd drug at its site of action.

Examples:

Propranolol reduces effect of salbutamol
Naloxone reduces effect of morphine

2- Pharmacokinetic interactions:

a. At absorption level:

Calcium salts, antacids decrease absorption of tetracyclines.

b. At distribution level:

Primarily due to displacement of one drug from its binding sites on plasma proteins by another drug.

Examples:

Toxicity of warfarin when displaced with aspirin.
Quinidine displaces digoxin leading to digitalis toxicity.

c. At metabolism level:

Enzyme inducers e.g. tobacco smoke, phenytoin and carbamazepine.
Enzyme inhibitors e.g. Cimetidine and Ketoconazole and valproic acid.

d. At excretion level:

Interactions involving excretion are important mostly in case of drugs actively secreted by tubular transport mechanisms. The alteration of urinary pH alters the process of reabsorption of the drug leading to increase or decrease excretion.

Examples:

Probenecid inhibits tubular secretion of penicillins and prolongs penicillin action.

Autonomic Nervous System (ANS)

Primary Neurotransmitters:

- Parasympathetic nervous system (cholinergic): Acetylcholine (Ach).
- Sympathetic nervous system (adrenergic): Norepinephrine (NE).
- Epinephrine (Adrenaline): is a chemical transmitter released by adrenal medulla, also acts as a transmitter in the sympathetic nervous system.

Types of the autonomic nerve fibers:

1. Cholinergic nerve fibers: ACh as chemical transmitter.
2. Adrenergic nerve fibers: NEP as chemical transmitter.

Sites at which ACh acts as a chemical transmitter:

1. All preganglionic neurons; both sympathetic and parasympathetic.
2. All postganglionic fibers of parasympathetic nerves.
3. The postganglionic sympathetic neurons of the eccrine sweat glands.
4. The nerve to adrenal medulla (sympathetic).
5. Motor end plate (neuromuscular junction) of skeletal muscles.
6. All autonomic ganglia; both sympathetic and parasympathetic.
7. Central nervous system.

Sites at which NEP acts a chemical transmitter:

It is the main transmitter of most of sympathetic postganglionic fibers, except those supplying sweat glands.

Steps involved in neurochemical transmission:

1. Biosynthesis of chemical mediator from precursors in the neuron.
2. Storage of the synthesized transmitter in a bound form readily to be dissociated as nerve impulses reach.
3. Release of chemical mediators from nerve endings.
4. Activation of postsynaptic membrane by altering permeability.
5. Termination the action of chemical mediator by enzymatic hydrolysis and/or reuptake.
6. Repolarization of postsynaptic membrane.

Receptors in ANS

The receptors in ANS are classified-according to the neurotransmitter that stimulates them into: cholinergic receptors (cholinoceptors) and adrenergic receptors (adrenoceptors).

1- Adrenergic receptors

Respond to epinephrine (EP) and norepinephrine (NE).

Subdivided into:

a. Alpha (α) receptors.
b. Beta (β) receptors.

A.Alpha (α) receptors

1. Subtypes: α1 and α2.

2. Signal transduction:

α1 receptors: are Gq-linked → stimulation of PLC→↑DAG and IP3→ ↑Ca2+.

α2 receptors: are Gi-linked → inhibition of adenylcyclase→ ↓c-AMP.

3. Sites and actions:

a) α1-receptors are found mainly in:

Smooth muscle fibers of:

1) Blood vessels (especially of skin and mucous membranes): Vasoconstriction which leads to ↑ peripheral resistance (PR) and ↑ABP.
2) Eye: Active mydriasis.
3) GIT and urinary bladder: Relaxation of wall and contraction of the sphincter.
4) Male sex organs: Ejaculation.
5) Uterus: Contraction.
6) Erector pili muscle (pilomotor muscle): Contraction.

b) α2-receptors are found in:

1) CNS: Inhibition of sympathetic outflow.
2) Presynaptic membrane of the adrenergic nerve terminals: (-)'ve feedback; inhibition of the release of NEP; they are called auto-receptors.
3) Pancreas: Inhibition of insulin release.
4) Platelets: Stimulation of platelet aggregation.
5) Kidney: Their stimulation decreases release of renin from the Juxtaglomerular cells.
6) α 2 receptors are also located at a number of postsynaptic sites, including certain regions of vascular smooth muscle: Contraction.

3. Agonists:

a) Non-selective agonists: Noradrenaline and adrenaline.
b) Selective α1-Agonists: Phenylephrine.
c) Selective α2-Agonists: clonidine and alpha methyldopa.

4. Antagonists:

a) Non-selective antagonists: Phentolamine and phenoxybenzamine
b) Selective α1-Antagonists: Prazosin.
c) Selective α2-Antagonists: Yohimbine.

B. Beta (β) receptors

1. Subtypes: β1- β2- β3.

1. Signal transduction:

All beta receptors are Gs-linked: stimulation of adenyl cyclase→↑ c-AMP.

2. Sites and actions:

a) β1 receptors:

1) Heart: Their stimulation increases force of myocardial contraction, increases heart rate and conductivity.
2) Kidney: Their stimulation increases release of renin from the Juxtaglomerular cells in the kidneys.

b) β2 receptors:

They are located in the smooth muscles of bronchi, blood vessels and intestine. Their stimulation leads to bronchodilatation, vasodilatation and relaxation of smooth muscles of intestine.

Actions of β2 receptors:

1- Generalized vasodilation especially coronary and skeletal muscle blood vessels.
2- Bronchodilation.
3- Relaxation of GIT and urinary bladder wall.
4- Relaxation of uterine smooth muscle.
5- Pancreas: Increase of insulin secretion.
6- Inhibition of release of histamine.
7- Increase glycogenolysis and gluconeogenesis in the liver.
8- Skeletal muscles → glycogenolysis →↑blood lactate, tremors, ↑uptake of K^+; inward shift of K^+ from blood into muscle cells leading to hypokalemia.
9- Presynaptic β2-receptors stimulate release of noradrenaline from adrenergic neurons; (+)'ve feedback circuit.

a) β3 receptors:

Increase the lipolysis in the adipose tissues.

3. Agonists:

a) Non-selective agonists: Adrenaline and isoprenaline
b) Selective β1 agonists: Dobutamine.
c) Selective β2 agonists: Salbutamol (albuterol), terbutaline and ritodrine.

4. Antagonists:

a) Non-selective antagonists: Propranolol.
b) Selective β1 antagonists: Atenolol, metoprolol - esmolol.
c) Selective β2 antagonists: Butoxamine.

Auto-receptors in sympathetic nervous system:

Presynaptic alpha (α2): ↓ Noradrenaline release from adrenergic neurons.
Presynaptic beta (β2): ↑ Noradrenaline release from adrenergic neurons.

2- Cholinergic receptors

Respond to Acetylcholine (Ach).

Subdivided into:

a. Muscarinic (M) receptors.
b. Nicotinic receptors.

A.Muscarinic (M) receptors

These receptors stimulated by ACh and named muscarinic because they stimulated also by muscarine "alkaloid present in certain mushroom".

1. Subtypes:

M1, M2, M3, M4 and M5 receptors.

2. Signal transduction:

M1 and M3: are Gq-linked → activation of phospholipase C, resulting in the generation of inositol-1, 4, 5-trisphosphate (IP3) and diacylglycerol (DAG) resulting in increased intracellular Ca2+.

M2: are Gi-linked → inhibition of adenylcyclase→↓c-AMP and activates of K+ channels.

3. Sites and actions:

- They are located mainly in GIT, heart, blood vessels, eye and secretory gland.
- Muscarinic receptors in the heart (M2): decrease cardiac contractility and heart rate.
- M3 muscarinic receptors causing secretion, contraction of visceral smooth muscle fibers and vascular relaxation.
- Stimulation of muscarinic receptors in the eye leads to miosis (decrease in pupil size) and decrease IOP. So, muscarinic agonists, e.g. pilocarpine are used in treatment of glaucoma.

Receptors	Sites	Agonists	Antagonists
M1	Gastric parietal cells: ↑HCl. CNS: ↑ Cognitive function. PNS ganglia: Depolarization.	ACh Methacholine Carbachol	Atropine and Pirenzepine
M2	Heart: ↓heart rate (bradycardia) ↓ contraction	ACh Methacholine Carbachol	Atropine
M3	1. Smooth muscle fibers of GIT and urinary tract: ↑ contraction 2. Exocrine Glands: ↑secretion 3. Endothelium: vasodilation 4. Male sexual organs: erection	ACh Methacholine Carbachol	Atropine

Auto-receptors in Parasympathetic Nervous System:

- ❖ M1 and M2 receptors are also present in the Presynaptic membranes of the cholinergic nerve terminals: Feedback inhibition of the release of Ach.

- ❖ Cholinergic agonist leads to stimulation of these receptors and hence, inhibition of the release of Ach. While, cholinergic antagonist leads to inhibition of these receptors and hence, increasing the release of Ach.

B.Nicotinic receptors

These receptors stimulated by ACh and named nicotinic because they also stimulated by nicotine. They are located in neuromuscular junctions (skeletal muscles), autonomic ganglia and adrenal medulla. They are of excitatory function.

They have2 major subtypes:

a. Nn-neuronal (ANS ganglia & adrenal medulla).
b. Nm-neuromuscular endplate (skeletal muscles).

Signal transduction:

Ligand-gated ion channel → open Na+ channels.

Receptors	Sites	Agonists	Antagonists
Nn-receptors	1-All autonomic ganglia (sympathetic and parasympathetic). 2-Adrenal medulla: ↑release of catecholamines	ACh Low conc. of nicotine	High conc. of nicotine Hexamethonium
Nm-receptors	Neuromuscular junction	ACh High conc. of nicotine	D-tubocurarine Galamine

Sympathetic nervous system
(Adrenergic nervous system)

It is the system in which NEP is the main chemical transmitter.

- NEP is a chemical mediator at all the postganglionic fibers of sympathetic nerves except the fibers which supply the sweat glands.
- EP is the emergency hormone secreted from the adrenal medulla.

Adrenergic drugs

They are classified into:

1. Sympathomimetics; adrenergic agonists.
2. Sympatholytics; adrenergic antagonists.

1. Sympathomimetics (adrenergic agonists)

Definition:

Drugs that produce effects similar to those produced by the sympathetic nervous system.

Classification:

A. These drugs are classified according to the chemical structure into:

1) **Catecholamines** (contain catechol nucleus):

a. Endogenous catecholamines: NEP, EP and dopamine (DA).
b. Non-endogenous catecholamines: dobutamine and isoproterenol.

2) Non catecholamines (no catechol nucleus): ephedrine, amphetamines.

Catecholamines

Distribution:

1. NEP:
•It is a chemical transmitter at adrenergic nerve end.
•It also presents in adrenal medulla (15-20%) and released in high conc. in case of pheochromocytoma (tumor in adrenal medulla).
•It also presents in different area of CNS.

2. EP:
•It is mainly present in adrenal medulla (80-85%).

3. Dopamine:
•It is mainly in CNS as in basal ganglia. It is a precursor of NEP and EP at other sites.

Function:

1. NEP: normal sympathetic function (transmitter).

2. EP: emergency hormone which promotes metabolism and blood flow to skeletal muscle and many other organs.
3. Dopamine: Its deficiency in basal ganglia leads to parkinsonial disease. Moreover it plays an active role in the action of some psychotropic drugs.

B. Adrenergic drugs can be classified according to their mechanism of action into:

1. Direct-acting agonists:
These drugs act directly on α or β receptors and produce effects similar to those occur following stimulation of sympathetic nerves.

Examples: Epinephrine, Norepinephrine, Isoproterenol and Phenylephrine.

2. Indirectly acting sympathomimetics:
They cause the release of the sympathetic neurotransmitter from the nerve terminals.

Example: Amphetamine.

3. Dual (Mixed)-action agonists:
These agents act either directly by stimulating the receptor or indirectly through release endogenous norepinephrine.

Example: Ephedrine.

A. Direct-Acting Agonists

1. Epinephrine (Adrenaline)

It is the catecholamine which is present in higher concentration in the adrenal medulla (80%-85%).
It acts on both types of adrenergic receptors; accordingly it is studied in details.

Pharmacokinetics:

a. Not given orally due to:
1. Poor absorption from the GIT.
2. Rapid destruction by intestinal juices.
3. Rapid metabolism by the liver enzymes; MAO and COMT.

b. Can not pass BBB.

Routes of administration:

It is used by the following routes:

1- S.C. producing local vasoconstriction that allows slow absorption.
2- Inhalation by nebulizers in bronchial asthma.
3- Eye drops in wide-angle glaucoma.
4- Nasal pack in treatment of epistaxis.
5- Intra-cardiac in cardiac arrest.

Mechanism of action: direct agonist stimulating **ALL** adrenergic receptors (β1, β2, β3 and α1, α2).

Pharmacological actions:

I- CVS:

a- Blood vessels:

1. V.C. of skin and mucous membrane blood vessels through α1-stimulation.

2. V.D. of skeletal muscle and coronary blood vessels through β2-stimulation.

- Small doses of EP affect the beta receptors which are more sensitive and persistent type.

- While, EP in large doses activates alpha receptors which is more abundant.

b- Cardiac muscle:

1. It increases the heart rate (+ve chronotropic action).
2. It increases the force of contraction (+ve inotropic action). Both effects are due to Stimulation of β1-receptors. Cardiac output is therefore increases.
3. It increases conductivity (+ve dromotropic effect) and may produce ventricular dysrhythmias.
4. It increases automaticity.

c- Blood Pressure:

- Generally, EP is very potent vasopressor agent.
- The effect of EP on blood pressure depends upon dose and rate Because its action on both α-and β-receptors; α is more predominant and β is more sensitive.

II- Respiratory system:

1- Bronchodilatation (β 2 effect).
2- Bronchial mucosa vasoconstriction "decongestant effect" (α 1 effect).

III- GIT:

1- Relaxation of the wall leading to decrease in tone and motility (β-and α- stimulation).
2- It causes constriction of the sphincters (α 1 effect).

IV- Urinary bladder:

It causes urine retention due constriction of sphincter of the bladder (α 1 effect). It relaxes the detrusor muscle (β2 effect).

V- Eye:

1. Topically on normal eye it produces vasoconstriction of conjunctival blood vessels, so it is used to relief decongestion.
2. Active mydriasis due to stimulation of α1 receptor on radial muscle.
3. In cases of open angle glaucoma, it decreases IOP as it reduces the production of aqueous humor by vasoconstriction of the ciliary body blood vessels.

VI- Metabolic effects:

The major metabolic effects of epinephrine are increased circulating concentrations of:
a) Glucose (hyperglycemia): is caused by liver glycogenolysis leading to hyperglycemia, and skeletal muscle glycogenolysis leading to increased blood lactic acid (β2-stimulation). Hyperglycemia may be also due to decreased insulin release (α2-effect); insulin secretion is inhibited (α2) and enhanced (β2) ⟹ the predominant physiological effect being inhibition.
b) Free fatty acids (hyperlipemia) due to stimulation of β3-receptors of adipose tissue.
d) Increase in the oxygen consumption.

VII- Anti-allergic:

- Epinephrine decreases the release of histamine from mast cells.
- It is a physiological antagonist of histamine.

Therapeutic uses:

1. Local:

1. To stop local bleeding in epistaxis.

2. Subcutaneous injection with local anesthetics: prolong action of local anesthetics due to vasoconstriction that decreases systemic absorption of local anesthetic.
3. Treatment of glaucoma.
4. Nasal decongestant in common cold.

2. Systemic:

1. Bronchial asthma due to stimulation of β2 receptors.
2. Cardiac arrest (Intracardiac injection).
3. Anaphylactic shock; lifesaving.

Adverse reactions:

1. Anxiety, palpitations, headache and tremors.
2. Increased blood pressure and possible cerebral hemorrhage.
3. Cardiac arrhythmias and angina pectoris.
4. CNS disturbances: Epinephrine can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor. However, these are largely due to the peripheral metabolic and cardiorespiratory effects.

Contraindications:

1. Hypertension.
2. Hyperthyroidism as it causes cardiac arrhythmias.
3. Angina pectoris.
4. Cardiac arrhythmias

2. Norepinephrine

It is the chemical transmitter at postganglionic sympathetic neurons (except sweat glands). It also presents at the adrenal medulla (15%-20%).
It acts similar to EP on the above mentioned α actions.

Pharmacologically it differs from EP in the followings:

1. It is mainly act on α 1&2 and beta 1 receptors.
2. It has a little or no effect on beta 2 receptors.
3. It increases both systolic and diastolic BP and produces a reflexed bradycardia.

Therapeutic uses:

1. Acute hypotension (IV).
2. Treat shock due to increase blood pressure; however, dopamine is better since it does not reduce the blood flow to the kidneys as does NEP.

Contraindications: Similar to those of epinephrine.

3. Phenylepherine

Synthetic selective α 1- agonist.
It is a vasoconstrictor the raises both systolic and diastolic blood pressure. It can induce reflex bradycardia.

Therapeutic uses:

1. It is used topically as a decongestant in various nasal preparations.
2. It is used topically as a mydriatic in ophthalmic preparations.

4-Clonidine

1. Centrally acting alpha 2 receptor agonist.
2. Activation of presynaptic α2 receptors in the lower brain stem leading to suppression of sympathetic outflow from the brain.

Effects: Reduces blood pressure and produces inhibition of sympathetic vasomotor centers.

Therapeutic uses:

1. Hypertension
2. Withdrawal symptoms of narcotics, alcohol and tobacco
3. In anesthesia; Dexmedetomidine – sedative effect – preoperative sedation.

5. α- Methyl Dopa

1. α-methyldopa is converted into α-methyldopamine by dopa decarboxylase then into α-methylnoradrenaline by dopamine β-hydroxylase.

2. α-methyl noradrenaline acts as α2-agonist centrally and peripherally (on presynaptic α2-receptors) leading to reduction in sympathetic outflow from CNS and reduction in noradrenaline release from adrenergic neurons.

Therapeutic uses:

Hypertension during pregnancy (drug of choice).

6. Selective β2 agonists

1. They are β2 selective agents
2. They relax smooth muscles of bronchi, uterus and blood vessels of skeletal muscle
3. They have less stimulant effect on heart which contains β1 receptors
4. They can be given in small doses by inhalation. This activates β2 receptors in bronchi
5. They are used in the treatment of asthma.

Selective β2 agonists:

a. Short acting: Salbutamol (albuterol), terbutaline.

b. Long acting: Salmeterol.

1. Salbutamol (albuterol):
Action: β 2 selectivity. Short acting agent with a rapid onset.

Therapeutic uses:

Bronchodilator. The inhaled versions produce the greatest local effect on airway smooth muscle with the least systemic side effects.
Place in therapy:

This is the fast-acting bronchodilator of choice in asthmatics. Can be given orally and by inhalation for treatment of acute and chronic asthma as well as parentrally for status asthmatics.

2. Salmeterol:

Action: β 2 Selectivity. Long-acting agent with a slow onset. It is not used as a rescue inhaler like albuterol.
Indications: It is used as a maintenance therapy to reduce the occurrence of bronchospasms in patient with chronic asthma.

Adverse effects of β2 agonists:

1. Skeletal muscle tremors.
2. Tachycardia.
3. Hypokalemia.
4. Regular use over prolonged periods may cause failure to control disease; Tolerance due to desensitization (down regulation) of β receptors.

2. Sympatholytics
Adrenergic antagonists

They Block or decrease the effects of sympathetic nerve stimulation**.**
They are classified according to their site of action into:

A. <u>Adrenergic receptor blockers</u>:

They act at the receptors of the effect organs:
1. Alpha-adrenergic blockers.
2. Beta-adrenergic blockers.
3. Mixed alpha and beta blockers.

B. <u>Adrenergic neuron blockers</u>:

They act the adrenergic nerve. They inhibit the biosynthesis, storage and/or the release of the adrenergic chemical transmitter.

A. Adrenergic receptor blockers

1. <u>Alpha-adrenergic blockers:</u>

They act by interrupting the actions of the catecholamines norepinephrine and epinephrine at the alpha receptors resulting in: relaxation of the smooth muscle in the blood vessels; increased dilation of blood vessels; and decreased blood pressure.
The decreased blood pressure will cause reflex tachycardia and postural hypotension.
Decrease tone in smooth muscle of bladder neck resulting in improved urine flow in benign prostatic hyperplasia (BPH).

<u>Classification:</u>

Alpha adrenergic blockers may be classified according to:

1. <u>Reversibility of binding:</u>

A- Irreversible alpha blockers:
These compounds bind covalently and non- competitively to alpha receptors e.g. phenoxybenzamine.

B- Reversible alpha blockers:
These compounds bind reversibly to the receptors and produce a competitive blockade e.g. phentolmine, tolazoline and prazosin.

2. Selectivity of binding:

a. Non-selective alpha blockers:

Phenoxybenzamine and Phentolamine
They block both α1 and α2 receptors.

b. Selective alpha blockers:

Selective α1: Prazosin, Terazosin and Doxazosin
Selective α2: Yohimbine

Selective alpha blockers

Selective competitive α1 blockers: Prazosin, Terazosin and Doxazosin.
They block mainly α1 receptors.
They decrease the peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscles.

Terazosin exhibits similar properties as prazosin but differ in:
a- Less potent.
b- Higher oral bioavailability.
c- Longer duration of action.

Therapeutic uses:

1. Hypertension.
2. Congestive heart failure.
3. Benign prostatic hyperplasia (BPH): they produce smooth muscle relaxation of prostate gland and bladder neck and improve renal flow.

Recently, the alpha 1 receptor were classified into, α 1A-receptors which present in bladder neck and prostate and α 1B in the vascular smooth muscles of the blood vessels.

Adverse reactions of selective α1-blockers:

1. **First Dose Effect**: Exaggerated hypotensive effect that can lead to syncope especially when patient stands after sitting or lying down (orthostatic or postural hypotension).

This can be minimized by starting with a small dose and increasing the dose gradually or the use of the drug at bed time.

2. Reflex tachycardia.
3. Mild sexual dysfunction in males.

2. Beta-adrenergic blockers

a. <u>Nonselective β blockers</u>: Propranolol, Labetalol, Sotalol and Timolol.

b. <u>Selective β1 blockers</u>: Atenolol, Esmolol, Metoprolol and Acetutolol.

Nonselective β blockers

1. Propranolol

It is a prototype of non- selective beta-adrenergic blockers.

Pharmacokinetics:

Propranolol is a highly lipophilic drug:

a) Well absorbed orally, may be given parentally.
b) Passes easily through B.B.B. and has marked CNS actions.
d) Has extensive 1st pass hepatic metabolism (it has low oral bioavailability that is why oral dose is much higher than the parenteral dose).

Pharmacological effects:

1. Heart: Propranolol decreases heart rate and cardiac contractility, hence reducing the cardiac output. It directly depresses SA and AV activity. It decreases cardiac work and oxygen consumption.
2. BP: Reduce blood pressure by combined effects on the heart (negative inotropic and chronotropic effects) and Reduction in the effect of the renin-angiotensin system.
3. Bronchoconstriction: as a result of β2 receptor blockade (Beta blockers are contraindicated in bronchial asthma).
4. Inhibition of hyperglycemia and hyperlipedimia-induced by catecholamine. It augments the insulin-induced hypoglycemia. Moreover, it mask the important hypoglycemic signs as tachycardia, anxiety and tremors.
5. ↓uptake of K+ by skeletal muscles, and may lead to "hyperkalemia", by blocking β2-receptors in skeletal muscles.
6. CNS actions: It reduces anxiety by blocking β1-receptors in CNS. Also, it reduces tremors mainly by blocking β2-receptors in skeletal muscles and mainly by CNS action (propranolol is lipophilic).

Therapeutic uses:

1. Hypertension.
2. Angina pectoris.
3. Cardiac tachydysrhythmia.

4. Hyperthyroidism: to control palpitations.
5. Pheochromocytomia when given in combination with alpha adrenergic blockers.
6. Migraine; (prophylaxis).
7. After acute myocardial infarction (AMI) to decrease size of infarction, treat arrhythmias, decrease cardiac work and myocardial oxygen requirements, and increase survival (decrease mortality rate).
8. To reduce portal pressure in portal hypertension due to bilharzial or alcoholic cirrhosis.

Adverse effects:

1. Bradycardia, AV blocks, Cardiac failure.
2. Bronchospasm.
3. Masking hypoglycemic manifestations in diabetic patient.
4. Possible sexual impairment in male.
5. Increase in LDL and decrease in HDL causing atherosclerosis (non-selective β blockers mainly).
6. Hyperkalemia especially in renal impairment.
7. CNS manifestations: sedation, sleep disturbances, depression.
8. Sudden stoppage of the therapy with beta adrenergic blockers may cause rebound effect which is serious effect. Accordingly, the drug must be gradually withdrawal over several weeks.

Contraindications:

1. Congestive heart failure and heart block
2. Asthma.
3. Diabetic patients.

Drug Interactions of Propranolol:

- HME inducers as barbiturates, phenytoin, and rifampin increase hepatic metabolism of propranolol thus reducing its activity (the dose of propranolol should be increased).

- HME inhibitors as cimetidine decrease hepatic metabolism of propranolol and may lead to marked adverse effects (the dose of propranolol should be reduced).

Drugs acting on Parasympathetic nervous system

Drugs acting on the parasympathetic nervous system (cholinergic drugs):

Classification:

According to their effect, cholinergic drugs are classified into:

1. Parasympathomimetics; cholinergic agonists: these drugs produce effects similar to that produced by ACh.

2. Parasympatholytics; cholinergic antagonists: these drugs block the effects of ACh.

Parasympathomimetics (Cholinergic agonists)

A. **Direct acting cholinergic drugs:**

They stimulate cholinergic receptors. They act as agonists on Muscarinic±Nicotinic receptors. They are classified into:

1. Choline esters:

Acetylcholine (natural).
Methacholine, Carbachol and Bethanechol (all are synthetic).

2. Natural Alkaloids:

Pilocarpine, and Muscarine (not used as a drug).

B. Indirect acting cholinergic drugs:

They do not stimulate cholinergic receptors by themselves but they inhibit hydrolysis of endogenous acetylcholine by inhibiting cholinesterases; then the accumulated acetylcholine stimulates Muscarinic+Nicotinic receptors.

- They include anticholinesterases (cholinesterase inhibitors);

both reversible and irreversible.

1. Reversible:

Neostigmine, Physostigmine and Edrophonium.

2. Irreversible:
Organophosphorous compounds like Parathion and Echothiophate.

Acetyl choline

Ach is not used as a drug due to the following reasons:

1. Its brief duration of action as its rapid hydrolysis.
2. Non selectivity as it acts on both muscarinic and nicotinic receptors.
3. Ineffective orally as it is a quaternary ammonium compound (not absorbed).

Pharmacological Actions of Ach:

According to the type of cholinergic receptors, two types of actions are known:

1. **Muscarinic actions:**

1. CVS.
2. Smooth muscle.
3. Exocrine glands.

2. **Nicotinic actions:**

1. All autonomic ganglia.
2. Adrenal medulla.
3. Neuro-muscular junctions (NMJ) of skeletal muscles.

1. Muscarinic actions:

1- CVS:

a. Heart (M2 receptors):

1. Negative chronotropic effect (decrease on the heart rate, bradycardia)
2. Negative inotropic effect (decreases the force of contraction).
3. Negative dromotropic (decreases A-V conduction).

b. Blood vessels (M3 receptors):

1. Vasodilatation of the blood vessels. which is due to release of endothelium derived relaxing factor (EDRF); now, it is characterized to be nitric oxide (NO).
2. This resulting in decreasing of the peripheral vascular resistance and the arterial blood pressure.

2. Smooth muscles:

a. GIT:
It increases tone and motility (peristalsis) of the wall and relaxes the sphincter. Also, it increases secretions.

b. Urinary bladder:
It contracts the muscles of the wall (detrusor muscle) and relaxes the sphincters (urination).

c. Bronchi:
Bronchoconstriction. It increases bronchial secretions.

d. Eye:
1. Circular muscles: contraction (miosis).
2. Ciliary muscles: contraction (accommodation for near vision).
3. Both 1 and 2 leads to a decrease in the intraocular pressure (IOP).

3. Exocrine glands:

Ach increases the secretion of all exocrine glands (e.g. bronchial, sweat, salivary and lacrimation) and HCl from gastric parietal cells.

2. Nicotinic actions:

Acetylcholine acts as a chemical transmitter on Nicotinic receptors found in autonomic ganglia-both sympathetic and parasympathetic and in the adrenal medulla (Nn receptors), and nicotinic receptors found in the neuro-muscular junctions (NMJ) of skeletal muscles (Nm receptors).

Neuro-muscular junctions (NMJ):

In a small dose Ach contract, the skeletal muscles (contraction). However, large dose leads to persistent depolarization and muscle flaccidity.

Physiological Responses to Cholinergic Stimulation

Tissue	Response
Eye: Sphincter muscle (iris) Ciliary muscle	 contraction - miosis contraction - near vision
Heart: SA node Atria AV node Ventricle	 decrease in HR decrease in contractility decrease in conduction ± block ± decrease in contractility

Lung: Bronchial smooth muscle Bronchial glands	 constriction increased secretion
Stomach: Gastric smooth Sphincters Gastric glands	 increased motility & tone relaxation increased secretion
Intestines Intestinal smooth Sphincters Intestinal glands	 increased motility & tone relaxation increased secretion
Bladder: Detrusor Trigone & internal sphincter	 contraction relaxation
Adrenal Medulla	increased secretion NA & A
Exocrine glands Salivary Lacrimal Sweat Glands	 increased secretion increased secretion increased secretion
Sexual organs	erection (male)

Parasympathomimetic Drugs

I-Directly acting parasympathomimetics:

1. Choline esters:

- These are esters of choline and all of them are derivatives from the parent compound Ach.
- They differ from each other in :

a) Selectivity to the cholinergic receptors.
b) Rate of hydrolysis by the choline estrases.

	Acetylcholine	**Methacholine**	**Carbachol**	**Bethanechol**
Source	Natural	Synthetic	Synthetic	Synthetic
Susceptibility to ChE	Hydrolyzed by true and pseudo cholinesterase	Hydrolyzed by true enzyme only	Not hydrolyzed by true or pseudo	Not hydrolyzed by true or pseudo
Muscarinic action	Non-selective	Selective on CVS	Selective on eye, GIT, and urinary bladder	Selective on GIT and urinary bladder
Nicotinic action	Present	Low nicotinic actions	Present	Almost no action
Duration	Very short	Longer than Ach	Long duration	Long duration

Therapeutic uses of choline esters:

The only clinically used choline ester is **Bethanechol**.
It is used in:
1) GIT disorders: paralytic ileus.
2) Urinary tract disorder: acute and chronic urine retention.

Side effects and toxicity of choline esters:

1. Bradycardia, heart block, hypotension.
2. Bronchospasm.
3. Stimulation of HCl secretion.
4. Tightness of urinary bladder.
5. Nausea, vomiting and abdominal cramps.
6. Visual disturbance.

2. Natural Alkaloids:

Pilocarpine:

- It is a tertiary amine. It penetrates the BBB.
- It is orally absorbed with longer duration of action as it does not metabolized by cholinesterases.

Pharmacological actions:

Direct muscarinic agonist with no nicotinic effect. Muscarinic actions as acetylcholine, but are marked on the smooth muscle fibres (eye, GIT, and urinary bladder), and on exocrine glands (sweat and salivary glands).

1. Eye: miosis- contraction of the ciliary muscle- ↓IOP.
2. GIT: contraction of the wall and relaxation of sphincter.
3. Urinary bladder: contraction of the detrusor muscle of the wall and relaxation of the sphincter leading to urination.
4. Sweat glands: increases sweat secretion glands); this action is known as "**diaphoresis**".
5. Salivary glands: increases salivation, an action known as "**sialagogue**" action.

Therapeutic uses:

1. Treatment of glaucoma alone or in combination with physostigmine (double miotic). It facilitates drainage of aqueous humor and hence a reduction in the IOP. It is considered as a drug of choice in the emergency lowering of IOP in both closed and wide-angle glaucoma.
2. Alternatively, with mydriatics to break adhesions between iris and lens.
3. Sialagogue to treat the dry mouth (Xerostomia).

Adverse effects:

1. Exaggerated parasympathetic stimulation.
2. Enter the brain and causes CNS disturbances (avoid in Parkinsonism).

II- Indirect parasympathomimetics (Anti-cholinesterases):

They inhibit cholinesterase enzyme which is responsible for metabolism of Ach.

1. **Reversible cholinesterase inhibitors**: Neostigmine and physostigmine.

2. **Irreversible cholinesterase inhibitors**: Organophosphorus compounds.

1. Reversible Anticholinesterases:

These drugs are classified according to the duration of action into:

A. Long acting (about 2-8 hours), carbamate derivatives:
Physostigmine, neostigmine and pyridostigmine: they attach at both sites of the enzyme, the anionic and esteratic sites.

1. **Neostigmine:**

Therapeutic uses:

1. Treatment of myasthenia gravis.
2. Antidote of curare poisoning.
3. GIT: paralytic ileus
4. Urinary bladder: retention of urine.
5. Glaucoma.

2. **Physostigmine:**

Therapeutic uses:

1. Glaucoma.
2. Adhesive iritis to cut adhesions between irris and lens in alternative with mydriatics.
3. To counteract mydriatic effect after use of parasympatholytics.
4. Atropine poisoning.
5. Alzheimer disease.

	Physostigmine	Neostigmine
Source	Natural: plant origin	Synthetic
Chemistry	Carbamate-Tertiary amine	Carbamate-quaternary ammonium

Kinetics	1- Well absorbed orally. 2- Passes BBB. 3-Rapid metabolism by ChE. 4- Short duration	1- Irregular oral absorption. 2- Does not pass BBB. 3-Slow metabolism by ChE. 4- Long duration.
Dynamics	1-Stimulate M&N receptors. 2- Specific on eye. 3- CNS stimulant.	1- Stimulate M&N receptors. 2- Specific on GIT and UB. 3- Direct Sk.M stimulant.
Therapeutic uses	1- Eye drops: a- Glaucoma. b- To counteract mydriatics. 2- IV in atropine poisoning. 3- Alzheimer disease.	1- Myasthenia gravis. 2- Curare poisoning. 3- Paralytic ileus. 4- Urine retention
Toxicity	1- Exaggerated ACh-like actions. 2- CNS convulsions.	1- Exaggerated ACh-like action. 2- No convulsions in CNS.
Treatment	1- Atropine. 2- Anticonvulsants	Atropine only

B- <u>Short acting (10-20 minutes), non-carbamate derivatives:</u>

<u>Edrophonium</u>

Its short duration of action is mainly due to its binding with ChE at the anionic site only. Its actions are similar to those of neostigmine, except that it is more rapidly absorbed and has a rapid onset and short duration of action (10-20 min).
It is similar to neostigmine as it has nicotinic and muscarinic actions of acetylcholine.

<u>Therapeutic uses:</u>

1. It is used in the diagnosis of myasthenia gravis.
2. Differentiation between cholinergic crisis and myasthenic crisis that may occur in myasthenia gravis.

Parasympatholytics
(Anticholinergic Drugs)

These drugs block cholinergic receptors, and are classified into:

1. <u>Muscarinic Receptor Antagonists:</u>

These drugs block muscarinic receptors and are also referred to as "anti-muscarinic drugs.

2. <u>Nicotinic Receptor Antagonists:</u>

These drugs block nicotinic receptors. They are subdivided into:

a) <u>Ganglion Blockers:</u>

These drugs block Nn receptors in autonomic ganglia and adrenal medulla. They are subdivided according to their mechanism of action into:

1. Competitive ganglion blockers: e.g. hexamethonium and trimetaphan
2. Depolarizing (non-competitive) ganglion blockers: e.g. nicotine large dose.

b) Neuromuscular Blockers:

These drugs block Nm receptors in neuromuscular junction of skeletal muscles leading to skeletal muscle relaxation. They are subdivided according to their mechanism of action into:

1. Competitive neuro-muscular blockers: e.g. d-tubocurarine.
2. Depolarizing (non-competitive): succinylcholine.

Muscarinic Receptor Antagonists

They are competitive antagonists (blockers) that compete with acetylcholine for muscarinic receptors.

Classification:

1. Natural Belladonna Alkaloids:

Source: they are obtained from the following plants: Atropa belladonna, Hyoscyamus niger, and Datura stramonium.
Chemistry: they are tertiary amine esters of tropic acid.
Examples: Atropine and L- Hyoscine (Scopolamine).

2. Synthetic Atropine and Hyoscine Substitutes (Derivatives):

They include; Homatropine, Pirenzepine, Ipratropium, Benztropine.

1. Natural Belladonna Alkaloids

Atropine

Mechanism of Action:

Atropine is a competitive antagonist of acetylcholine at muscarinic receptors. The action of atropine is reversible and can be overcome by increasing the concentration of acetylcholine or any other muscarinic agonist or by the use of anticholinesterase.

Pharmacological Actions:

A. Antimuscarinic action:

1. **<u>CVS:</u> (M2)**

a. <u>Heart rate:</u>

- Atropine produces different effects on the cardiovascular system, depending on the dose.

- At low doses, the predominant effect is a decreased cardiac rate (bradycardia). On the past, this effect was thought to be due to central activation of vagus nucleus, the effect is now known to result from blockade of the M1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release.

- With higher doses of atropine, the M2 receptors on the SA node are blocked, and the heart rate decreases transiently, before tachycardia develops.

- The brief period of bradycardia results from blockade of the M1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release.

b. <u>Blood Pressure</u>:

- Arterial blood pressure is unaffected at therapeutic doses of atropine. However, at toxic levels, atropine will dilate the cutaneous vasculature (atropine flushing) which may be a compensatory reaction to permit the radiation of heat to counteract the atropine induced fever.

- Atropine reverses the hypotensive effect of large doses of acetylcholine, i.e. ACh reversal.

2. **<u>Smooth muscles</u>:(M3)**

a. GIT:
It causes relaxation of the wall (decreases tone and motility; antispasmodic effect) and contraction of the sphincter, leading to constipation.

b. Bronchi: bronchodilatation.

c. Urinary bladder:
It causes relaxation of the muscle wall (detrusor) and contraction of the sphincter, leading to urine retention.

d. Eye:
1. Passive mydriasis (due to the paralysis of the circular muscle).
2. Cycloplegia (loss of accommodation for near vision) due to paralysis of the ciliary muscle.

3. Loss of light reflex.
4. The produced mydriasis leads to closure of canal of Schlemm. This will result in closed angle glaucoma.

3. Exocrine glands:(M3)

Atropine decreases all secretions (except milk, and bile).

1. **Lacrimal glands:** atropine decreases lacrimation causing dryness of the eye (xerophthalmia).
2. **Salivary glands:** atropine decreases salivary secretion leading to dry mouth (xerostomia).
3. **Bronchial glands:** atropine decreases bronchial secretions.
4. **Gastric glands:** atropine decreases gastric secretion (both volume of secretion and HCl content). Pirenzepine, a selective M1 antagonist reduces gastric acid secretion and has a clinical value in controlling peptic ulcer.
5. **Sweat glands:** atropine decreases sweat secretion. Inhibition of sweat secretion can cause elevated body temperature
6. **Toxic doses** of atropine cause a rise of body temperature known as **atropine fever** which is due to sweat depression.

B. Actions on the CNS:

1. Small doses: cause mild stimulation of vagal and respiratory centers.
2. Repeated small doses or higher doses lead to CNS stimulation and produce restlessness and irritability, delirium, disorientation and hallucination.
3. Repeated large doses the stimulation is followed by a depression.
4. Atropine has a direct depressant effect on parkinsonial tremors.

Therapeutic uses:

1. Preanesthetic medication as it decreases both salivary and bronchial secretions.
2. Examination of fundus of the eye: Shorter-acting antimuscarinics (cyclopentolate and tropicamide) have largely replaced atropine due to the prolonged mydriasis observed with atropine (7–14 days versus 6–24 hours with other agents).
3. Peptic ulcer (Pirenzepine)**.**
4. Parkinsonism (Benzotropine).
5. Bronchial asthma (Ipratropium Bromide).
6. Incontinence of urine (nocturnal enuresis).
7. Antidote for organophosphorus Poisoning.
8. Antagonizes unrequired muscarinic actions of neostigmine in myasthenia gravis.

Adverse effects:

1- Constipation due to relaxation of smooth muscles of the GIT.
2- Retention of urine.

3- Tachycardia.
4- Blurred vision.
5- Palpitations, hot dry skin (atropine flushing) and hallucinations.
6- CNS stimulation: agitation and delirium.

Atropine toxicity

Cause of toxicity:

The toxicity may result from over dosage in therapy or mostly by eating datura plant.

Symptoms:

1. Dryness of mouth, very difficult talking and swallowing.
2. Hot dry skin and increased body temp.
3. Disturbance in vision (passive mydrasis + cyclopelgia).
4. Weak pulse and rapid palpitation.
5. Difficulty in micturation.
6. Abdominal distension.
7. Restlessness, excitement and confusion, disorientation and hallucination.
8. In severe cases circulatory and respiratory failure and death.

Treatment of atropine toxicity:

1- Artificial respiration, oxygen and Diazepam for convulsions.
2- Gastric lavage.
3- Ice bag for fever.
4- Antidote: Physostigmine IV.

2. Atropine substitutes

These drugs are more specific and with lower side effects than the parent atropine. They include:

1- **Scopolamine (hyoscin):**

- Similar to atropine in actions but:

a. With more prominent central effects.
b. Longer duration of action.
c. Mainly used for motion sickness.

2- Homatropine, cyclopentolate and tropicamide:

- Used in ophthalmology as rapidly acting mydriatic with short duration.

2- Propantheline:

- Synthetic agent that is used as antispasmodic and anti-diarrheal agent.

3- Ipratropium:

- Antimuscarinic that is given by inhalation for treatment of bronchial asthma.

4- Benzatropine:

- Synthetic drug that is used in treatment of parkinsonism.

5- Pirenzepine and telenzepine:

- M1 antagonist used in treatment of peptic ulcers.

7- Emepronium (cetiprine) and oxybutynin (uripan):

- They decrease motility of urinary bladder and lead to spasm of sphincters, accordingly are used in urinary incontinence and nocturnal incontinence.

1. Skeletal Muscle Relaxants

Major Events in Neuromuscular Transmission:

1. Motor neuron depolarization causes action potential to travel down the nerve fiber to the neuromuscular junction.
2. Depolarization of the axon terminal causes an influx of Ca^{2+}.
3. Ca2+ triggers fusion of the synaptic vesicles and release of neurotransmitter (Acetylcholine; ACh).
4. ACh diffuses across the synaptic cleft and binds to post-synaptic ACh receptor (AChR) located on the muscle fiber at the motor end-plate.
5. Binding of ACh to AChRs opens the channels causing an influx of Na, depolarization of the sarcolemma that travels down the t-tubules.
6. This ultimately causes the release of Ca2+ from the sarcoplasmic reticulum - CONTRACTION.
7. Finely ACh in is hydrolyzed (inactivated) by acetylcholinesterase (AChE).

Definition of Skeletal Muscle Relaxants:

These drugs acting on skeletal muscles leading to skeletal muscle relaxation.

Neuromuscular blockers:

1. Depolarizing muscle relaxants.
2. non-depolarizing muscle relaxants

	Non-depolarizing (Competitive)	Depolarizing (noncompetitive)
Mechanism of action	Competing with Ach at Nm-R.	They cause initial depolarization→ followed by persistent depolarization →transmission failure →receptor blockage.
Examples	Tubocurarine Gallamine	Succinylcholine

B-Drugs that increase transmission:

Cholinesterase inhibitors:

1- Reversible:

e.g. neostigmine, physiostigmine

2- Irreversible:

e.g. organophosphorus insecticides

Both will lead to accumulation of Ach at neuromuscular junction.

Neuromuscular blockers

Definition:

These drugs block Nm receptors in neuromuscular junction of skeletal muscles leading to skeletal muscle relaxation.

Classification:

They are classified according to their mechanism of action into:

1. Competitive neuro-muscular blockers: e.g. curare, gallamine, pancuronium, vecuronium, atracurium.
2. Depolarizing (non-competitive) neuro-muscular blockers: succinylcholine.

A. Competitive neuro-muscular blockers:

- They Compete with ACh and antagonized by ChE inhibitors
- Prototype of Non-depolarizing is tubocurarine (new generation: pancuronium and gallamine).

Mechanism of action:

- They block nicotinic receptors (at the same site at which acetylcholine binds) competitively resulting in inhibition of sodium channels and excitatory post-synaptic potential.
- Because of their competitive nature, the relief of the block can be achieved by increasing ACh levels at the synaptic cleft (i.e. use cholinesterase inhibitors).

They are classified according to their duration of action into:

1. Long acting (2 hours):
d. tubocurarine, pancuronium

2. Intermediate acting (1 hour):
Vecuronium, rocuronium and atracurium

3. Short acting (15 min): e.g. Mivacuronium

Pharmacokinetics:

- They must be given by injection because they are poorly absorbed orally.
- They do not cross the BBB.
- Metabolism through kidney or liver **except** mivacurium and atracurium by plasma cholinesterase.

Therapeutic uses:

1. Adjuvant in surgical anesthesia to provide muscular relaxation.
2. Orthopedic procedures for alignment of fractures
3. Electro-convulsive therapy (ECT): treatment of psychiatric disorders (psychotic patient).
4.Facilitate laryngoscope, bronchoscope and osphagoscope.

Drug Interactions:

1. Cholinesterase inhibitors decrease the effectiveness of competitive agents.
2. Aminoglycoside antibiotics (e.g. streptomycin) decrease ACh release by competing with Ca^{++} and increase action of competitive drugs.
3. Calcium channel blockers increase the actions of competitive drugs by decreasing the amount of ACh released.
4. Halogenated carbon anesthetics (e.g. Isoflurane) enhance neuromuscular blockade by: decreasing excitability of motoneurons, increasing muscle blood flow (as they produce peripheral VD).

1-Tubocurarine
It leads to flaccid paralysis.

Sequence of Paralysis:
Small muscles relaxed firstly and lastly the inter costal muscles. Recovery in the reverse order.

In addition to NMB it produces:
1) Ganglionic blockade.
2) Histamine releaser.
3) Both 1and 2 lead to hypotension and bronchospasm.

Curare toxicity:
1. Peripheral respiratory failure.
2. Decrease blood pressure.
3. Bronchospasm.

Treatment of curare toxicity:
1. Artificial respiration.
2. Neostigmine (cholinesterase inhibitor, direct stimulant action on skeletal muscle.
3. Atropine prior to neostigmine to block muscarinic action.
4. Adrenaline to antagonize effect of histamine release.

2- Gallamine (Flaxedil):
- Synthetic curare substitute
- Its action like curare but:

a) Less active
b) Weaker ganglionic blocker.
c) Weaker histamine releaser.
d) It has atropine like action on heart.

3- Atracurium:
- It has shorter duration than curare.
- No ganglionic blocking effects
- Slight histamine release.

B. Depolarizing muscle relaxants:

Succiunyl choline (Suxamethonium):

Prototype of depolarizing agent is succinylcholine (only depolarizing drug in clinical use).

Mechanism of Action: Similar action to ACh, but longer acting.

PhaseI (Depolarizing): Succiunylcholine combines with nicotinic receptors→ depolarization of motor end plate → initial muscle twitching → Persistent depolarization → Flaccid paralysis.

Phase I block is augmented not reversed by anticholinestrases.

Phase II (Desensitization Block): Continuous exposure to succinylcholine depolarization decreases and the membrane becomes repolarized, but the membrane cannot be depolarized by Ach as long as succinylcholine present →desensitization of the membrane.
Phase II block can be reversed by anticholinesterase.

Pharmacokinetics:

Duration of action is ultra-short (several minutes) because it is rapidly broken down by plasma cholinesterases (must be administered by continuous infusion).

Pharmacological actions:

1. Skeletal muscles: fasciculation, followed by flaccid paralysis.
2. Hyperkalemia: can lead to cardiac arrest.
3. Eye: it increases intraocular pressure, contraindicated in glaucoma.
4. GIT: it increases intra-gastric pressure which can lead to regurgitation of gastric content to esophagus.
5. CVS: arrhythmia.

Adverse effects:

1. Hypotension.
2. Decreased tone and motility in GI tract.
3. Depolarizing agents can cause increased K efflux in patients with burns, trauma, or denervation and lead to hyperkalemia.
4. **Prolonged apnea:** in some individual with the genetic deficiency of the pseudochlinesterase enzyme.
5. **Malignant hyperthermia**: this is also a genetic abnormality in sarcoplasmic reticulum characterized by excessive calcium release which leads to muscle rigidity and increase in heat production especially when administered with halothane.

Malignant hyperthermia

Inability to bind calcium by sarcoplasmic reticulum in some patients due to genetic abnormality in sarcoplasmic reticulum characterized by excessive calcium release. This leads to intense muscle spasm, rise in temperature.

Drugs Triggering Malignant Hyperthermia:

1. General anesthesia e.g. halothane, isoflurane and Sevoflurane
2. Neuromuscular blockers e.g Succiunyl choline (Suxamethonium)

Manifestations:

Generalized muscle rigidity, marked temperature elevation, increased CO_2 production, Tachycardia, Tachypnea, combination metabolic and respiratory acidosis, severe cardiac arrythmias and hyperkalemia.

Treatment of Malignant hyperthermia:

- Stop triggering inhalation agents/succinylcholine.
- Hyperventilate high flow 100% O_2
- Rapid cooling of the body and dantrolene.
- Treat hyperthermia, acidosis, and arrhythmias

Directly acting skeletal muscle relaxants

Dantrolene

Mechanism of action:
It blocks directly the sarcoplasmic reticulum; this leads to decrease release of calcium from sarcoplasmic reticulum.

Therapeutic uses:
1- Spastic muscle lesions.
6- Malignant hyperthermia of succinylcholine.

Centrally acting skeletal muscle relaxants

Diazepam

It is a Benzodiazepine drug that probably facilitates the actions of $GABA_A$ in the CNS and spinal cord.

Baclofen

It is $GABA_B$ agonist. Primarily used in the treatment of spasticity associated with spinal cord injury.

Anti-spasticity drugs (Spasmolytic Drugs)

Drugs that used to relieve skeletal muscle spasm & bring them from hypertonic state to normal muscle tone.

They include:

1- Central muscle relaxant.
2- Dantolene.

Myasthenia gravis

Definition:

It is a neuromuscular disease characterized by weakness and marked fatigability of skeletal muscles.

Pathophysiology:

It is an autoimmune disease caused by production of antibodies against the nicotinic acetylcholine postsynaptic receptors at the neuromuscular junction of skeletal muscles. This causes their degradation and makes fewer receptors available for interaction with the neurotransmitter.

Symptoms:

- Eye lid drooping (ptosis).
- Impaired speech (dysarthria).
- Difficulty swallowing (dysphagia).
- Double Vision (dipoplia).
- Easily fatigued, quick recovery with rest.
- Waddling gait.

Diagnosis:

Edrophonium test:

Edrophonium is a rapid onset, short acting acetylcholinesterase inhibitor.
A 10 mg edrophonium hydrochloride syringe and a 2 mg atropine syringe are prepared. Atropine is prepared for immediate use in case cholinergic crisis occurs.
After a neurologic examination and recording of vital signs, first 2 mg edrophonium is injected intravenously. After waiting 45 seconds and ensuring that no adverse reactions occurred, the remaining 8 mg of edrophonium is also injected.
A patient suffering from myasthenia gravis experiences improvement in muscle strength and endurance with repetitive movements, while normal persons do not feel any difference.
The effects of edrophonium last around 10 minutes. The edrophonium allows accumulation of acetylcholine (ACh) in the neuromuscular junctions, and makes more ACh available to the muscle receptors, thereby increasing muscle strength in myasthenia gravis.

Cholinergic crisis:

A cholinergic crisis is an over-stimulation at a neuromuscular junction due to an excess of acetylcholine (ACh), as of a result of inhibition of the AChE enzyme, which normally breaks down acetylcholine.
Excessive accumulation of acetylcholine (ACh) at the neuromuscular junctions and synapses causes symptoms of both muscarinic and nicotinic toxicity. These include cramps, increased salivation, lacrimation, muscular weakness, paralysis,

muscular fasciculation, diarrhea, and blurry vision, sinus bradycardia, and respiratory failure. Atropine should be available during the test.

Treatment of Myasthenia gravis:

A. Oral anticholinesterases:

neostigmine or neostigmine substitutes as pyridostigmine and ambenonium (oral).

They prolong acetylcholine action by inhibiting cholinesterase.

Overdose of anticholinesterases causes severe weakness (cholinergic crisis).

Muscarinic side-effects, e.g. colic and diarrhoea, are common; oral atropine (antimuscarinic) 0.5 mg helps to reduce these side effects.

B. Atropine (oral): to avoid the undesired muscarinic actions.

C. Immunosuppressive drugs as glucocorticoids (cortisol) may be needed.

Indication of Atropine use in treatment of myasthenia gravis:

- Sometimes atropine is given with neostigmine in myasthenia gravis to block unrequired muscarinic actions.
- It is important to know that the two drugs must not be used together at the same time as both gives additive bradycardia.
- In this case, Neostigmine must be preceded by atropine.

	Myasthenic crisis	Cholinergic crisis
Cause	The dose of neostigmine is less than required. **(under-treatment)**	The dose of neostigmine is more than required leading to sustained depolarization. **(over-treatment)**
Diagnosis by IV Edrophonium	Leads to improvement of muscle weakness.	Leads to worsening of muscle weakness.
Treatment	Increase the dose of neostigmine.	Decrease the dose of neostigmine.

Cardiac disorders

Drug therapy of Angina pectoris

Definition:

Angina pectoris is the classical symptom of ischemic heart. It is usually due to imbalance between myocardial oxygen supply and demand. It is characterized by sudden, severe, pressing chest pain starting substernal and radiate to left arm.

Classification of angina:

1. Exertional angina (Stable, Atherosclerotic or Classic angina)

It is characterized by:

1) Cardiac pain which develops on exertion e.g. exercise, eating, cold weather or emotional stress.

2) Significant fixed coronary stenosis (atherosclerotic) and/or excess myocardial demand.

ECG shows depressed ST segment.

2. Unstable angina.

If the cardiac pain happens at minor exertion or at rest and with increased frequency, it is called unstable angina. It is a medical emergency as it may progress to myocardial infarction.

3. Variant or prinzmetal's angina:

1. Patient develops cardiac pain at rest and ECG shows elevated ST segment.
2. It is due to vasospasm of coronary artery with resulting decrease of coronary blood flow.
3. It may occur spontaneously or may be induced by exposure to cold, emotional stress or vaso-constricting drugs e.g. ergot derivative drugs.

1. Organic nitrates

Examples:

Nitroglycerine, isosorbide mononitrate and isosorbide dinitrate.

Mechanism of action:

Nitrates converts in vascular smooth muscle cell into nitric oxide (NO). NO then activates guanylyl cyclase enzyme which increases the cellular level of cGMP & cGMP-dependent protein kinase. This leads to decrease in both myosin light chain phosphorylation and cytosolic calcium concentration resulting in relaxation of vascular smooth muscles.

Pharmacological effects:

1. **At low concentrations:**

- Nitroglycerine preferentially dilates the veins more than the arterioles, with consequent reduction of preload, decrease of left and right ventricular chamber size, and end diastolic pressure.
- This leads to, decrease in the cardiac work and oxygen demand of the heart and relieve of anginal chest pain.
- Nitrates may also improve myocardial blood flow by dilating collateral coronary blood vessels so that blood redistributes from normal to ischemic regions.
- Arteriolar dilatation at these concentrations may affect arterioles of the face (causing flushing) and meningeal arterioles (causing pulsating headache).

2. **At higher concentrations:**

Nitrate induced venodilatation is associated with arteriolar dilatation and reduced peripheral resistance leading to reduced blood pressure, cardiac output and compensatory sympathetic reflex tachycardia.

Therapeutic uses:

1- Angina pectoris: all types of anginas**.**

a. In acute attack:

Sublingual nitroglycerine is the drug of choice. Nitroglycerine buccal spray is also available. It acts in about 1-2 minutes. Sublingual route allows absorption of drug rapidly from buccal mucosa, with avoidance of extensive first pass effect if swallowed orally. The dose (0.3, 0.4, 0.6 mg) may be repeated at 3-5 minutes intervals. If, pain is not responding to three tablets or lasting more than 20 minutes, this may represent infarction that needs medical intervention.

b. In between attacks:

To prevent a new attack, any of the following nitrate's preparations are indicated:

1. Short-acting nitrates as nitroglycerine sublingual or isosorbide dinitrate sublingual to be taken 5 minutes before any activity that may precipitate angina.
2. Long-acting nitrates to be taken as a maintenance therapy such as nitroglycerine in the form of: oral sustained release capsules, ointment, or transdermal patches, oral isosorbide dinitrate.

2- Heart failure, as a vasodilator especially if heart failure is associated with cardiac ischemia.

2- **Hypertensive emergency,** it is given by IV route.

Adverse effects:

1. Pulsating headache (Throbbing headache).
2. Reflex tachycardia.

3. Postural hypotension (nitrate syncope). It is treated by change the position of the patient (let head down and leg elevated).
4. Marked fall in blood pressure and even death if given concomitantly with sildenafil (Viagra). Both drugs are vasodilators.
5. Tolerance: frequently repeated or continuous exposure to high dose of organic nitrates leads to marked decrease in their pharmacological effects. To avoid tolerance, nitrate free intervals for 8-12 hours each day.

2. Beta adrenergic blockers

Mechanism of action:

They prevent angina through reduction of heart rate, myocardial contractility and to lesser extent blood pressure leading to reduction of myocardial oxygen requirement during exertion and stress. They prolong the life in patients with coronary disease.

Therapeutic uses:

1.They are effective in the prophylactic treatment of classic and unstable angina.
2.They are not used in variant angina;
In prinzmetal's (vasospastic) angina, use of beta blockers opens the way for catecholamines to act on unopposed coronary α- receptors which may increase coronary spasm. Therefore, β-blockers are not preferred in prinzmetal's vasospastic angina.

3. Calcium channel blockers

Mechanism of action:

Calcium channel blockers inhibit the L-type calcium channels in the cardiac and vascular smooth muscle of coronary arteries.
This will lead to decrease calcium influx into myocardium and vascular smooth muscles:

a. Decrease calcium influx into myocardium will lead to:

- Decrease myocardial contractility and heart rate causing a decrease in myocardium oxygen requirements.

b. Decrease calcium influx into vascular smooth muscles (arterioles) will lead to:

- Vascular relaxation and decrease in peripheral resistance (after load) causing a decrease in oxygen requirement.
- Relief of coronary spasm.

Therefore, in patients with coronary vasospasm (e.g. prinzmetal's or vasospastic angina), they are the drugs of choice.

Pharmacological effects:

Verapamil and diltiazem:

In addition to their vasodilator effect, they decrease the heart rate through a depressant effect on SA node and slowing the A-V nodal conduction. Also, they have a negative

inotropic effect. Therefore, it is not advisable to combine any of them with β-blockers as may lead to heart block or heart failure.

Nifedipine:
Has no A-V blocking activity and is more potent as arterial vasodilator. So, its reducing effect on blood pressure may be associated with reflex sympathetic stimulation and tachycardia. Accordingly, it is advisable to combine it with a β-blocker in patients with angina.

Therapeutic uses:

1. Angina pectoris: prophylaxis in all types of anginas, drug of choice in vasospastic angina
2. Hypertension.
3. Supraventricular tachycardia (verapamil or diltiazem, but not nifedipine).
4. Migraine headache (verapamil as a prophylaxis).

Adverse effects:

1. **Nifedipine**
   Headache, flushing, nausea, ankle edema, dizziness, reflex tachycardia.

2. **Verapamil and Diltiazem**
   Similar to nifedipine except that they do not cause reflex tachycardia.
   Constipation mainly with verapamil.
   They can lead to AV block if given with beta blockers, and digitalis.

Pharmacology of Blood

Anticoagulant Drugs

Definition: Anticoagulants are drugs used in prevention and treatment of thromboembolic diseases.

Classification:
1. Parenteral anticoagulants: heparin, hirudin and lipirudin.
2. Oral anticoagulants: warfarin.

1. Parenteral anticoagulants

Heparin

1. Unfractionated Heparin; High Molecular Weight Heparin (HMWH):

Source:
It is of animal origin: naturally, heparin is present in mast cells with histamine and it is prepared from bovine lung and porcine intestine.

Chemistry:
It is a mucopolysaccharide molecule, strongly acidic and electro-negatively charged (acidity and negative charge are essential for the anticoagulant activity of heparin).

Pharmacokinetics:

Absorption: heparin is not absorbed orally.

Route of administration: heparin is given IV (bolus and infusion) and SC but never IM to avoid hematoma.

Distribution: heparin cannot pass placental barrier and is safe during pregnancy.

Metabolism:
Heparin is metabolized by the liver and partly excreted unchanged in urine. It is not excreted in breast milk. So, it is not contraindicated in lactation.

Mechanism action:
Heparin activates antithrombin III known as heparin cofactor which in turn inhibits thrombin and other coagulation factors as factor Xa. Heparin is an indirect thrombin inhibitor.

Pharmacological effects:
It is direct anticoagulant drug.

Advantages:

1. Rapid onset.
2. given IV or SC.
3. Can be given in pregnancy and lactation.
4. No drug interactions.
5. Acts both in vivo and in vitro.

Disadvantages:

1. Short duration: due to rapid clearance.
2. Given only by injection and needs careful monitoring of the dose and accordingly the patient must be hospitalized.
3. Antiplatelet action (inhibits platelet aggregation) in large doses.

Control of Dose:

1. Activated Partial Thromboplastin time (aPPT):

- Normal: about 30-40 seconds.
- After heparin: should be 2-2.5 times the normal value.

2. Coagulation Time (Clotting Time):

- Normal: 5-7 minutes.
- After heparin: should be 2-2.5 times the normal value.

Therapeutic uses:

1. Deep venous thrombosis (DVT) and pulmonary embolism.
2. Unstable angina.
3. Treatment of acute myocardial infarction.
4. Treatment of cerebral thrombosis
5. Prophylaxis therapy to prevent thrombosis in high-risk patients as orthopedic surgery and balloon angioplasty in cardiac patients.

Adverse effects:

1. Hemorrhage is the most serious adverse reaction.

Treatment: a. Stop heparin. b. Protamine sulphate: it is the specific antidote of heparin. It is strongly basic and electro-positively charged (acts by chemical antagonism). c. Fresh blood transfusion.

2. Hypersensitivity reactions.
3. Thrombocytopenia: which may be mild transient reversible, or severe due to heparin-induced platelet aggregation or heparin-induced antiplatelet antibodies.
4. Thrombosis: chronic use of heparin reduces antithrombin III activity leading to increased risk of thrombosis.
5. Transient reversible osteoporosis (may cause spontaneous fractures).

2. Low Molecular Weight Heparin (LMWH):

Examples:
- Enoxaparin, Dalteparin - Nadroparin.
- They are obtained by enzymatic depolymerization of UFH.

Advantages over UFH:
1. High bioavailability after SC injection and long duration allowing once daily injection.
2. It is bind to antithrombin III and activate it to inhibit factor X (Xa) mainly and have less effect on other coagulation factors; so they are less liable to induce hemorrhage.
3. Predictable pharmacokinetics, so the doses are easily calculated and no need for monitoring by aPTT, and can be used as out-patient therapy.

2. Oral anticoagulants

Warfarin

Source: Synthetic.
Chemistry: Coumarin derivative.

Pharmacokinetics:
Absorption: absorbed orally.

Distribution: It is highly bound to plasma proteins (99%). It passes placental barrier and may cause teratogenicity. It should be avoided during pregnancy.

Metabolism: It is extensively metabolized by liver microsomal enzyme CYP2C9. So, it is liable for drug interactions.

Mechanism of action:
It inhibits vitamin K epoxide reductase which is needed for production of vitamin K – dependent coagulation factors prothrombin (factor II), factors VII, IX, and X. Warfarin is considered a vitamin K antagonist.

Pharmacological effects:
It is indirect anticoagulant, acting in vivo only.

Advantages:
1. Easy route of administration.
2. Long duration of action (4-7 days).

Disadvantages:

1. Delayed onset (1-2 days): treatment should be started by co-administration of heparin and warfarin for about 4-5 days then heparin is stopped and warfarin, is continued alone after being sure of its anticoagulant action (PT should be 2-2.5 times its normal value).
2. High susceptibility for drug interactions.
3. Contraindicated in pregnancy.

Control of the dose:

1- Prothrombin time (PT):

- Normal: 12-15 seconds.
- After oral anticoagulants: PT should be 2-2.5 times the normal value.

2- International Normalized Ratio (INR): it is a ratio between PT of the patient / PT of control. It should be 2-3 after oral anticoagulation.

Adverse effects:

1- Hemorrhage from any sits is the most serious adverse effect.

Treatment:

a. Stop the drug.
b. Vitamin K is the specific antidote, e.g. vitamin K1 IV.
c. Fresh blood transfusion.

2- Gut upsets: anorexia, nausea, vomiting, and diarrhea.

3- Allergic reactions: skin rash.

4- Teratogenicity (abnormal bone development).

5- Skin necrosis is rare but serious (may be due to rapid elimination of anticoagulant proteins C and S before coagulation factors are eliminated leading to liability of formation of thrombi in skin blood vessels, it is prevented by co-administration of heparin).

6- Drug interactions.

	Heparin	Warfarin
Source	Animal origin	Synthetic
Chemistry	Mucopolysaccharide	Coumarin derivative
Pharmacokinetics	• Not absorbed orally. • Given only IV or SC but never IM. • Does not pass placental barrier and not excreted in breast milk. • Metabolized by the liver.	• Absorbed orally. • Highly bound to plasma proteins. • Pass placental barrier and minimally excreted in breast milk. • Metabolized by the liver.
Mechanism of action	Activates antithrombin III and inhibits active factor X, thrombin and other factors.	Inhibits vitamin K epoxide reductase thus inhibiting synthesis of prothrombin and factors VII, IX, and X.
Pharmacological actions	• Direct Anticoagulant. • Acts both in vivo and in vitro. • Rapid onset and short duration.	• Indirect Anticoagulant. • Acts only in vivo. • Slow onset and long duration.
Control of dose	aPTT and Coagulation time	PT and INR
Antidote	Protamine sulphate IV	Vitamin K IV
Safety during pregnancy	Safe	Unsafe

Antiplatelet Drugs (Antithrombotic Drugs)

Definition:
Drugs used to prevent platelet aggregation. They are particularly effective in prophylaxis against arterial thrombosis such as coronary thrombosis.

Mechanism of action of Antithrombotic drugs:

1. Inhibition of TXA2 synthesis:
Through inhibition of TXA2 synthetase (platelet COX).

Aspirin:
Infantile (pediatric) doses of aspirin (75- 150 mg / day) cause irreversible inhibition of TXA2 by acetylation of the enzyme.

2. Inhibition of ADP-dependent pathway:
These drugs inhibit binding of ADP-to-ADP receptors on platelets and so, inhibit activation of GP Ilb/IIIa receptors and inhibit binding of platelets to fibrinogen and to each other.

Ticlopidine and Clopidogrel

Adverse effects: bleeding (no specific antidote). Ticlopidine may cause neutropenia but clopidogrel has lower incidence of neutropenia.

3. GP Ilb/IIIa receptor blockers:
These drugs inhibit binding of fibrinogen to GP Ilb/IIIa receptors on platelets and thus inhibit platelet aggregation.

Abciximab (monoclonal antibodies agaist GP Ilb/IIa receptors).

Adverse effects: bleeding and thrombocytopenia.

4. Prostacyclin analogue:
Epoprostenol: it has direct VD effect and antiplatelet effect.

5. Drugs increasing platelet c-AMP:
Dipyridamole: inhibit phosphodiesterase leading to increased platelet c-AMP.

Dipyridamole
It is ineffective alone and is used in combination with aspirin. It also a vasodilator and myocardial stimulant both directly due to increased cardiac c-AMP and reflexly following vasodilatation and hypotension.

Therapeutic uses of antithrombotic drugs:

Prophylaxis against thrombo-embolism (especially arterial) in old age, stable and unstable angina, after myocardial infarction and cerebrovascular thrombosis.

Adverse effects:

Bleeding, no specific antidote, blood transfusion may be required.

Central Nervous System (CNS)

Local anesthetics

Definition:
Drugs that cause loss of pain sensation in a specific part of the body when applied locally without loss of consciousness.

Mechanism of action:
They reversibly inhibit the nerve conduction through blockade of Na+ channels i.e. they stabilize the membrane action potential. Small nerve fibers are more susceptible.
Pain sensation disappears first → cold → warmth → touch → deep pressure.

Prolongation of the action of local anesthetic is done by:
Administration of a vasoconstrictor drug; the used commonly vasoconstrictor is epinephrine that leads to:
1. Delay absorption of the local anesthetic from site of injection.
2. Increase duration of action of local anesthetic agent.
3. Decrease bleeding and provide bloodless field during the surgery.
4. Decrease the dose of the local anesthetic and accordingly, decrease its systemic toxicity.

Factors affecting the action of local anesthetics:
1. **Lipid solubility**: is an important characteristic. Potency is related to lipid solubility, because 90% of the nerve cell membrane is composed of lipid. This improves transit into the cell membrane.

2. **pH influence:** local anesthetics are weak bases. Decrease in pH shifts equilibrium toward the ionized form, delaying the onset action. Lower pH, solution more acidic, gives slower onset of action (poor penetration).

3. **Vasoconstrictors:**

Most LA produce some degree of vasodilation, and they may be rapidly absorbed after local injection. Vasoconstrictors decrease the systemic toxicity and increase the safety margin of local anesthetics by reducing their rate of absorption.
vasoconstrictors are frequently added to LA to enhance their potency and prolong their duration of action. Adrenaline is the most commonly used vasoconstriction.

Pharmacokinetics:

Absorption:
LA generally have good absorption from mucous membranes.

Factors influencing absorption:
1. Site of injection (vascularity).
2. Dose of LA.
3. Specific drug characteristics.

e.g. tendency to produce vasodilation.
4. Presence of vasoconstrictor (e.g., epinephrine, phenylephrine) - not needed with cocaine.

Effects of vasoconstrictors;

1. Decrease rate of systemic absorption and decrease systemic toxicity.
2. Increase local drug concentration and increase neuronal uptake of LA.
3. Increase local duration of action.
4. Bloodless field.

Distribution:
LA can be widely distributed to all parts of the body including CNS.

Metabolism:

1. Ester type LA
Hydrolysis by pseudocholinesterase in plasma.

2. Amide type LA
Hydrolyzed by liver microsomal enzymes (P450).

Excretion: in urine.

Methods of local anesthesia:

1- Surface anesthesia (Topical anesthesia): local anesthetic is applied to the skin or mucous membranes.

2- Infiltration anesthesia: through direct subcutaneous injection into or around the area needed to be anesthetized. It is used in minor surgery.

3- Block anesthesia: local anesthetic agent is injected close to a single nerve or a plexus of nerves supplying the area to be anesthetized. It used for surgical, dental procedures and for analgesia.

4- Spinal anesthesia: local anesthetic is injected in the subarachnoid space between the second and fifth lumbar levels to reach the spinal roots supplying the area to be anesthetized. It is used for surgery to lower limbs, pelvis or in obstetrics.

5-Epidural anesthesia:
Injection into epidural space usually at lumbar or sacral levels. Used like spinal and also painless childbirth. Unwanted effects similar to that of spinal anesthesia.

Classification of local anesthetics:

According to the chemical structure, two types:

1- Esters: esters are metabolized by pseudocholinesterase in plasma. One of the main breakdown products is para-amino benzoate (PABA) which is associated with allergic phenomena and hypersensitivity reactions and inhibit sulfonamides.

2- Amides: amides are metabolized by liver microsomal enzymes. Hypersensitivity reactions to amide local anaesthetics are extremely rare.

	Esters	**Amides**
Duration of action	Short duration	Long duration
Toxicity	Low systemic toxicity	More systemic toxicity
Examples	Cocaine Procaine Benzocaine Tetracaine	Lidocaine Mepivacaine Bupivacaine

Duration of action of local anesthetics:

The duration of action varies from less than 1 hour (procaine), 1-2 hours (lignocaine) or more than 2 hours (bupivacaine).

Adverse effects:

1. CNS: it may be manifest as CNS stimulation or depression:

Stimulation:
Restlessness, tremors, muscle twitching and convulsions.
Depression:
Coma and respiratory failure.

2. CVS:

- They cause myocardial depression; they depress contractility, excitability and conduction.
- Hypotension due to vasodilatation (direct and myocardial depression) except cocaine which cause hypertension as it inhibits uptake of NEP.

3. Hypersensitivity reactions: it is more common with ester type of local anesthetics.

Toxicity from Local Anaesthetic Drugs:

when excessive blood levels occur. usually due to:

1. Accidental rapid intravenous injection.
2. Rapid absorption, such as from a very vascular site
3. Absolute overdose if the dose used is excessive.

Signs and Symptoms of LA Toxicity:

1. It involves the CNS and CVS. In general (CNS) is more sensitive to LA than the CVS. Therefore, CNS manifestations tend to occur earlier. Brain excitatory effects occur before the depressant effects.

2. **CNS signs & symptoms:**
   A. **Early or mild toxicity**: light-headedness, dizziness, tinnitus, numbness, confusion and drowsiness.
   B. **Severe toxicity**: Severe convulsions may be followed by coma with respiratory and cardiovascular depression.

3. **CVS signs & symptoms:** With the exception of cocaine, all local anesthetics are vasodilators. Severe toxicity: Collapse is due to the depressant effect of the LA acting directly on the myocardium. Severe and intractable arrhythmias can occur with accidental I.V. injection.

   Cocaine blocks norepinephrine reuptake at sympathetic junctions and the drug's vasoconstricting actions contribute to cardiovascular toxicity. When cocaine is used as a drug of abuse, its cardiovascular toxicity includes severe hypertension with cerebral haemorrhage, cardiac arrhythmias, and myocardial infarction.

Treatment of Toxicity:

1. Assure adequate ventilation and oxygen supplementation
2. Seizures: diazepam.
3. Hypotension: Trendelenburg position (head down, legs up).
4. I.V. fluids.
5. Vasopressors.
6. Treatment of dysrhythmia.

Commonly used local anesthetics:

1. **Ester type local anesthetics:**

Cocaine

Its use is limited to surface or topical anesthesia.
It has potential for abuse and addiction.
No need for epinephrine administration with cocaine because cocaine causes vasoconstriction due to inhibition of active uptake of NEP.

Procaine

It is not useful for surface anesthesia as it is not absorbed from mucous membrane.
It has slow onset, short duration and weak potency.
Epinephrine used to prolong effect.
It is used for infiltration, spinal and for nerve block anesthesia.
No addiction and less toxic than cocaine.

Tetracaine

It is used for all types of local anesthesia including surface anesthesia for eye, nose and throat anesthesia. Its effect is longer acting and more potent than procaine.

2. Amide type local anesthetics:

Lidocaine

It is the most commonly used local anesthetic.
It has rapid onset, long-lasting effect.
It is used for all types of local anesthesia.
It is also used as antiarrhythmic drug.

Mepivacaine

It has rapid onset and more prolonged effect than lidocaine.
It is effective in all types of local anesthesia except topical.
It is not used in obstetric anesthesia as fetus poorly metabolizes mepivicaine.

General anesthetics

Definition:

- Drugs that cause a reversible depression of CNS resulting in loss of the sensation as well as loss of consciousness to a sufficient degree to perform a surgery.

- General anesthesia is a state characterized by unconsciousness, analgesia, amnesia, skeletal muscle relaxation, and loss of reflexes. Drugs used as general anesthetics are CNS depressants with actions that can be induced and terminated more rapidly than those of conventional sedative-hypnotics.

The main considerations during administration of general anesthetics:

1- Minimizing the potential adverse effect of the anesthetic agent.
2- Maintaining the physiological hemostasis during surgical procedures
3- Improving postoperative effects to overcome the surgical stress response.

Induction, maintenance and recovery from general anesthesia:

Induction:
It is the period of time from the onset of administration of the potent anesthetic to the development of eff ective surgical anesthesia in the patientis achieved usually by an IV anesthetic like thiopental which produces unconsciousness. Then, additional inhalation or intravenous anesthetics are given to produce the desired depth of surgical anesthesia. Skeletal muscle relaxants e.g. pancuronium may also be given concomitantly to facilitate intubation and produce muscle relaxation.

Maintenance: It provides a sustained surgical anesthesiais the period where the patient is surgically anesthetized and anesthesia is maintained by administering volatile anesthetics because these agents allow minute-to-minute control over the depth of anesthesia. IV infusions of various drugs may also be used during the maintenance phase. The patient's vital signs and response to various stimuli are monitored continuously throughout the surgical procedure to carefully balance the amount of drug inhaled and/or infused with the depth of anesthesia.

Recovery: is achieved by withdrawal of the anesthetic mixture and the return of patient to conscious state. It is the time from discontinuation of administration of anesthesia until consciousness and protective physiologic reflexes are regained.

Stages of anesthesia:
Stage I, ***Analgesia***: loss of pain sensation but patient is still conscious.
Stage II, ***Excitement***: the patient appears to be delirious and excited. Amnesia occurs, reflexes are enhanced, and respiration is typically irregular, rise and irregularity in blood pressure, and incontinence may occur.

Stage III, ***Surgical anesthesia***: the patient is unconscious and has no pain reflexes, regular respiration, blood pressure is maintained, and relaxation of skeletal muscles, pupil is fixed and surgery proceed in this stage.
Stage IV, ***Medullary Depression***: severe depression of respiratory and vasomotor centers that requires mechanical and pharmacologic support to prevent death.

Mechanism of action:

- ❖ General anesthetics may act through GABA-A receptor, K channels or NMDA receptors.
- ❖ Inhaled anesthetics, etomidate, and propofol facilitate γ-aminobutyric acid (GABA)-mediated inhibition at GABAA receptors.
- ❖ Ketamine possibly acts via its antagonism of the action of the excitatory neurotransmitter glutamic acid on the N-methyl-d-aspartate (NMDA) receptor.

Classification of general anesthetics:

1. Inhalational anesthetics:

a. Volatile liquids: e.g. halothane, isoflurane, enflurane, sevoflurane, and desflurane.
b. Gases: e.g. nitrous oxide.

2. Intravenous anesthetics:

a. Barbiturates: e.g. ultra-short acting: thiopental
b. Non-barbiturates: e.g. propofol, etomidate, and ketamine.

1. Inhalational anesthetics

1. Halothane:

It is a potent anesthetic but weak analgesic.
Rapid induction and rapid recovery.
It is commonly used in children as it is well tolerated and with less side effects in children.

Pharmacokinetics:

Up to 80 % of halothan is eliminated unchanged via the lungs. The rest of the drug is metabolized by liver microsomal enzymes to form tri-fluoroacetic acid which may alter several proteins in the liver that may lead to halothane induced hepatic necrosis.

Therapeutic uses:

It is used for induction and maintenance of anesthesia.

Characteristic effects of halothane:

1. It can sensitize the myocardium to EP leading to arrhythmia
2. Halothane has a bronchodilator effect and can be used in asthmatic patients.
3. It causes uterine relaxation, so unsuitable as anesthetic for labor and vaginal delivery. But it can be used for delivery of retained placenta after labor.
4. It can produce fulminant hepatic necrosis.

5. It can cause malignant hyperthermia in genetically susceptible patients when used in combination with the non-depolarizing skeletal muscle relaxant succinylcholine.
6. Low cost.

2. Isoflurane:

1. Rapid induction and rapid recovery. It is used for induction and maintenance of general anesthesia.
2. No hepatotoxicity.
3. Potent coronary vasodilatation. So, it is safe in patients with ischemic heart disease.
4. It causes uterine relaxation.

3. Enflurane:

1. Induction and recovery are relatively slow.
2. Less potent than halothane.
3. Its use has been reduced as it may induce seizures.

4. Desflurane:

1. Very rapid induction and recovery. It is widely used for outpatient surgery
2. Irritant to the airways and induces cough, salivation and bronchospasm.

5. Sevoflurane:

1. Rapid smooth induction and rapid recovery
2. It is non-irritant to the airway and potent bronchodilator.
3. it suitable for induction anesthesia in children. It is replacing halothane for this purpose.

4. **Nitrous oxide**

1. It is weak anesthetic but potent analgesic.
2. N_2O is used as adjunct to other inhalational or intravenous anesthetics to decrease the dose required from other anesthetic.
3. It does not depress either respiration or cardiac function. Also, it does not produce skeletal muscle relaxation.
4. Very rapid induction and rapid recovery.
5. Nitrous oxide is frequently used at concentrations of 30-50 % in combination with oxygen for analgesia, particularly in dental surgery. However, nitrous oxide at 80 % (without other agents) cannot produce surgical anesthesia.

2. Intravenous anesthetics

They are used for rapid induction of anesthesia. Anesthesia may then be maintained with an appropriate inhalation agent. IV anesthetics may be used as the sole agents for short procedures or administered as infusions to help maintain anesthesia during longer procedures. In lower doses, they may be used to provide sedation.

1. Thiopental

1. It has ultra-short duration of anesthesia.
2. It is used for induction of anesthesia.
3. The anesthetic effects of thiopental are terminated by redistribution from the brain to other tissues (skeletal muscle and adipose tissue), but hepatic metabolism is required for elimination from the body.
4. It produces a rapid induction and smooth rapid recovery with small doses.
5. Large doses delay recovery due to redistribution.
6. It is potent anesthetic but weak analgesic.
7. It cause hypotension due to VD and decreased COP.

2. Propofol

1. Rapid induction and rapid recovery similar to thiopental.
2. It is used for induction, maintenance of anesthesia in minor surgery and as a sedative in intensive care unit.
3. It has anti-emetic effects.
4. It produces pain on injection and this can be reduced by simultaneous administration of lidocaine.
5. It is safe to use in pregnant women and does not produce bronchospasm.

3. Ketamine

1. It produces dissociative state (dissociative anesthesia) in which the patient is unconscious but seems to be awake; the eyes remain open, the patient is sedated, immobile, does not feel pain, and does not respond.
2. Induction is rapid and recovery is slow and is accompanied by bad dreams and hallucinations.
3. It is used mainly in children and young adults for short procedures.
4. It increases blood pressure, heart rate and COP due to inhibition of peripheral and central catecholamine uptake.
5. It acts by blocking of NMDA receptors.

4. Etomidate

1. It causes little or no decrease in blood pressure. So, it is suitable for patients at risk of hypotension or hypovolemia. It causes pain at site of injection.
2. It causes myoclonic movements which can be reduced administration of benzodiazepines.
3. Inhibition of cortisol secretion.

Pre-anesthetic medications

Definition:
These drugs given before administration of anesthesia.

Purposes for their use:
1. Calm the patient and reduce anxiety.
2. Produce loss of memory(amnesia).
3. Decrease preoperative pain.
4. Decrease the dose of the anesthetic agent. So, decease side effects of the used anesthetic.
5. Decrease the volume and acidity of gastric contents.

The commonly used Pre-anesthetic medications:
1- Benzodiazepines (sedatives): as diazepam to decrease anxiety and facilitate amnesia.

2- Anti-histaminic drugs (H1-antagonists): as diphenhydramine to prevent allergic reactions.

3- H2-blockers like ranitidine to reduce gastric acidity.

4- Opioids like morphine or fentanyl as analgesic.

5- Atropine to prevent bradycardia and reduce respiratory secretion.

6- Skeletal muscle relaxants (Neuromuscular blockers): they are given after induction of anesthesia to facilitate tracheal intubation and surgical procedures.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Definition:
NSAIDs are drugs that have analgesic effect (relieve pain), antipyretic effect (treat fever) and anti-inflammatory effect.

Mechanism of action of NSAIDs:
NSAIDs inhibit cyclooxygenase enzymes leading to inhibition of synthesis of prostaglandins and thromboxanes which are involved in; pain, fever and inflammation.

Types of cyclooxygenases:

1. Cyclooxygenase 1 (COX-1):
It is a constitutive enzyme that exists under normal conditions in most cells such as GIT, Kidneys, and platelets where it catalyzes the formation of essential prostaglandins involved in normal physiological functions like gastric secretion and kidney function, but not pain or inflammation.

2. Cyclooxygenase 2 (COX-2):
It is induced in damaged tissues by inflammatory stimuli like interleukin-1 and tumor necrosis factor leading to the formation of inflammatory prostaglandins within the tissues.

Inhibition of COX-1 and COX-2 enzymes by NSAIDs:
It leads to inhibition of prostaglandin production. This reduces inflammation, but also affects other body systems such as gastric mucosal integrity and renal homeostasis.

- **Inhibition of COX-2** by NSAIDs leads to inhibition of PGs production and reduce inflammation.
- **Inhibition of COX-1** is responsible for their GIT toxicity, renal dysfunction.

✓ ***NSAIDs differ in the extent of inhibition of COX-1 and COX-2 enzymes:***

This is often expressed as the COX-2:COX-1 selectivity ratio.
1. The older traditional NSAIDs such as aspirin, indomethacin and ibuprofen inhibit the two enzymes to a similar degree.
2. Etodolac and meloxicam inhibit COX-2 more than COX-1.
3. Newer agents like celecoxib are highly selective COX-2 inhibitors.

Non selective COX inhibitor lead to gastric ulceration or bleeding, and renal dysfunction.

Selective COX-2 inhibitors are expected to decrease inflammation but not cause gastric ulceration or bleeding. But, there is no cardio-protection.

Classification of NSAIDs:

1.Non-COX-selective NSAIDs:

1. salicylates e.g. aspirin.
2. Acetic acid derivatives e.g. indomethacin, diclofenac, and etodolac.
3. Propionic acid derivatives e.g. ibuprofen and naproxen.
4. Enolic acid derivatives (oxicams) e.g. piroxicam and meloxicam.
5. Fenamic acid derivatives e.g. mefenamic acid.

2.COX-2-selective inhibitors: celecoxib (celebrex).

3. Para-aminophenols: acetaminophen (paracetamol).

Common adverse effects of NSAIDs:

1. Gastritis and peptic ulceration with bleeding.
2. Acute Renal Failure in susceptible.
3. Salt and water retention and edema.
4. Analgesic nephropathy.
5. Prolongation of gestation and inhibition of labor.
6. Hypersensitivity reactions.

Salicylates
Aspirin (acetyl salicylic acid)

Mechanism of action of Aspirin:

Aspirin-mediated inhibition of cyclooxygenase (COX).

Pharmacological effects:

1. Analgesic effect:

Aspirin is effective in pain of low to moderate intensity especially of musculo-skeletal origin, but not visceral pain.

Aspirin by decreasing synthesis of prostaglandins which sensitize the nerve endings (nociceptors) to the effect of inflammatory chemical mediators like histamine and bradykinin.

2. Antipyretic effect:

Aspirin by its prostaglandin inhibitory effect lowers the elevated body temperature.

Prostaglandin E2 is pyrogenic and their release centrally at hypothalamic level can elevate body temperature.

In fever, endogenous pyrogens (like cytokines) are released secondary to tissue damage, inflammation or infection. They circulate in the blood reaching the brain and stimulating prostaglandin release.

On the other side, acute aspirin poisoning elevates body temperature (hyperthermia) due to aspirin-induced uncoupling of oxidation and phosphorylation process. So, energy released is not utilized in ATP formation and is released as heat.

3. Anti-inflammatory effect:

Prostaglandins play a major role in inflammatory reactions. Aspirin inhibits synthesis of prostaglandins and exert its anti-inflammatory effect. Aspirin covalently binds to COX-1 & COX-2 and irreversibly inhibits their activity.

4. Antiplatelet effect:

- They inhibit thromboxane synthesis by blocking the enzyme cyclooxygenase-1 (COX-1).
- Thromboxane A2 is a potent stimulator of platelet aggregation.
- Aspirin, an irreversible COX inhibitor, is particularly effective.
- Because platelets lack the machinery for synthesis of new protein, inhibition by aspirin persists for several days until new platelets are formed. Antiplatelet effect of aspirin = 3 – 7 days (life of platelet).

Dose of Aspirin:

- Low dose (pediatric dose) of aspirin (75-100 mg/day) cause irreversible inhibition of TXA2 by acetylation of the enzyme.
- Low-dose aspirin inhibits cycloxygenase-1(COX-1) in such a way that only TXA2 production is inhibited and not of PGI2.
- Low dose aspirin therapy administered during the second and third trimesters of pregnancy is safe.

5. Cardiovascular:

- Aspirin by inhibiting cyclooxygenases irreversibly inhibits platelet production of TXA2. TXA2 enhances platelet aggregation which is the initial step in thrombus formation. Therefore, aspirin is described to have an antiplatelet effect; **cardio-protective effect**.

- Aspirin is used to prevent further infarcts in persons who have had 1 or more myocardial infarcts. The drug is used extensively to prevent transient ischemic attacks (TIAs), ischemic stroke, and other thrombotic events.

6. Gastrointestinal tract:

PGs (generated via COX-1):

1.Inhibit stomach acid secretion,

2. Stimulate mucus and HCO3- secretion, vasodilation and therefore,
3. They are cytoprotective for the gastric mucosa.
Therefore, NSAIDs with COX-1 inhibitory activity will produce opposite effects, leading to: gastric distress, gastric bleeding, sudden acute hemorrhage (effects are dose-dependent).

7. <u>Respiratory system:</u>

At higher doses, aspirin acts directly on respiratory center in the medulla leading to hyperventilation and respiratory alkalosis corrected usually by the kidney.
In toxic doses, central respiratory paralysis may develop leading to respiratory acidosis due to continued production of CO2.
In asthmatic patients, aspirin may provoke or worsen asthma in about 5% of these patients.

8. <u>Kidney:</u>

- Renal prostaglandins have a physiological role in normal kidney function and maintenance of renal blood flow.
- COX generated PGs (TxA2, PGF2, PGI2 (glom), PGE2 (medulla), powerful vasodilators) can maintain RBF and GFR by their VD effect, also they regulate Na^+ and water excretion (inhibition of Na+ tubular reabsorption, promote Na excretion in CT and via action on ADH).
- NSAIDs tend to promote Na+ retention and can therefore increase Bp. Can counteract effects of many anti-hypertensives (diuretics, ACE inhibitors and ARBs).
- Patients (particularly elderly and volume depleted) are at risk of renal ischemia with NSAIDs.

9. <u>Gestation:</u>

PGs are involved in the initiation and progression of labor and delivery. Therefore, inhibition of their production by NSAIDs can prolong gestation.

10. <u>Urate excretion:</u>

The effect of aspirin on uric acid excretion is dose dependent. Small doses (1-2 gm/day) reduce its renal excretion while, large doses (more than5gm/day) increase its excretion (uricosuric effect).

<u>11. Other effects of NSAIDs</u> (mechanisms less understood): Decreased risk of fatal colon carcinoma.

Pharmacokinetics:

Absorption:
Aspirin is well absorbed from stomach and upper intestine while its absorption when given rectally is incomplete.

Distribution:
In blood, it binds to plasma proteins (80-90%) causing displacement of other bound drugs (drug interaction). It can cross both placental barrier and blood brain barrier.

Metabolism and excretion:
It is metabolized in the liver and excreted in urine as glycine and glucuronide conjugates.
Alkaline urine accelerates aspirin excretion and prevents its tubular reabsorption.

Therapeutic uses:

1. Antipyretic; treatment of fever
2. Analgesic; relieve of pain e.g. headache, joint pain, neuralgia, toothache, and dysmenorrheal.
3. Anti-inflammatory; treatment of inflammatory conditions such as rheumatoid arthritis, osteoarthritis, and gout.
4. Antiplatelet; low doses are used prophylactically to reduce the risk of cerebral and coronary thrombosis especially in patients with chronic stable angina, or recurrent myocardial infarction.
5. External application; as a keratolytic agent, treat corns, warts.
6. Cancer chemoprevention; there is growing evidence of increased expression of COX-2 in multiple epithelial tumors to the extent that it may affect the prognosis of the tumor. The frequent use of aspirin has been found associated with reduced risk of colon cancer.

Adverse effects:

1. At therapeutic doses:

1. Nausea and vomiting.
2. Heart burn.
3. Peptic ulcer.
4. Increase bleeding tendency.
5. Hypersensitivity reactions e.g. skin allergy and bronchial asthma in asthmatic patients.
6. Long-term use of NSAIDs may cause impairment of renal function due to inhibition of prostaglandin synthesis in the kidney.

7. In febrile children with viral infection e.g. influenza or chicken pox, a syndrome called **Rey's syndrome** may occur which involves hepatic injury and encephalitis. **Paracetamol** is safely given as antipyretic in this condition
8. If given during pregnancy (especially last trimester), it may prolong the gestation period as it affects uterine prostaglandin production. Also, it may increase the risk of postpartum hemorrhage.

2. Salicylism:

Definition:
Mild intoxication following repeated use of large doses and disappear once drug is stopped.

Manifestations:
- Nausea and vomiting.
- Tinnitus.
- Dizziness.
- Sweating and hyperventilation.

3. Acute salicylate poisoning:
It develops from excess dose intake either accidentally, or as a suicidal attack.

Manifestations:
- Hallucination, delirium, convulsions and coma.
- Hyperthermia (uncoupling of oxidative phosphorylation).
- Marked acid-base disturbances (respiratory and metabolic acidosis).
- Electrolyte imbalance.
- Dehydration.
- Respiratory failure, coma and death.

Treatment:
- I.V. fluids.
- In severe cases, hemodialysis may be required.

Drug interactions:

Drug displacement from plasma protein binding:

Aspirin is highly bound to plasma proteins (about 90%) and therefore it may displace other highly bound drugs to plasma proteins and increase their free concentration. This may lead to increased efficacy and even developed toxicity of displaced drugs such as:

a. Warfarin (an oral anticoagulant) leading to severe hemorrhage.

b. Tolbutamide (oral hypoglycemic) leading to hypoglycemia.

Paracetemol (Acetaminophen)

- Paracetemol: weak anti-inflammatory effect, but used for its mild analgesic and antipyretic effects.
- Analgesic and antipyretic (inhibits PGs centrally).
- weak anti-inflammatory (less effect on COX peripherally).
- Well-absorbed and without GIT irritation.

Pharmacokinetics:

Absorption:

Well-absorbed and without GIT irritation.

Metabolism and excretion:

After ingestion of paracetamol, about 90% of the compound undergoes metabolism in the liver in conjugation with glucuronic acid (50-60%), sulfuric acid (25-35%) and cystine (approximately 3%) to form pharmacologically inactive metabolites, which are eliminated with urine. A small amount of the drug (about 5%) is eliminated in an unchanged form by kidneys. Subsequent 5% of paracetamol is subjected to N-hydroxylation in the liver with the involvement of cytochrome P450 enzymes (particularly CYP2E1) to form a toxic metabolite N-acetyl P-benzoquinone imine (NAPQI), which is very quickly inactivated by glutathione sulfhydryl groups
and excreted with urine as mercapturic acid.

Therapeutic uses:

1. It is used as analgesic and antipyretic.
2. It is the analgesic and antipyretic of choice in children with viral infections.
3. It is used as alternative to aspirin in patients with peptic ulcer, aspirin hypersensitivity, bleeding tendency.
4. paracetamol is the drug of choice in pregnant women.

Adverse effects:

1. At normal doses, paracetamol has no significant adverse effects.
2. At high doses, severe hepatotoxicity results, paracetamol becomes a dangerous and life-threatening drug because a highly reactive NAPQI metabolite covalently binds to hepatocyte macromolecules leading to impairment of enzymatic systems and structural and metabolic damage to the liver (potential lethal hepatic necrosis).

Treatment of paracetamol overdose:

N-Acetylcystein acts by detoxifying NAPQI. It repletes glutathione stores and may directly conjugate with NAPQI.

Other NSAIDs

Indomethacin: used in refractory fevers.
Common adverse effects: gastric bleeding, ulceration, CNS most common: hallucinations, depression, seizures, headaches, dizziness.

Proprionic acids: better tolerated. Ibuprofen, naproxen widely used for inflammatory joint disease and few side-effects.

Oxicams: long half-life , once daily, used for inflammatory joint disease.

Narcotic analgesics

Opium:
Milky exudates obtained from unripe seeds of poppy plant (papaver Somniferum) which contains morphine and other components.

Opiate:
Any naturally occurring opioid derived from opium (e.g. morphine).

Opioids:
Drugs that have opium or morphine like effects. Any naturally occurring, semi-synthetic or synthetic compound that binds specifically to opioid receptors and shares the properties of one or more of the naturally occurring endogenous opioids. They characteristically relieve pain but their analgesic activity is associated with drowsiness and mood elevation.

Narcotic:
It is often used to denote an opioid but also widely used to describe drugs of addiction and hence includes non-opioid compounds.

Opioid receptors:
- Opioid receptors are the binding sites for opioids not only in the CNS, but also in the periphery (e.g. nerve plexuses in GIT).
- In the CNS, they are found in high concentrations in the limbic system, thalamus, hypothalamus, brain stem and spinal cord.

Types of receptors:
1- MOP- μ (mu): μ1 (supraspinal analgesia) and μ2 (spinal analgesia, respiratory depression, euphoria, miosis, sedation and constipation).
2- KOP- κ (kappa): spinal analgesia, hallucination, and dysphoria.
3- DOP- δ (delta): analgesia (supraspinal and spinal) analgesia.

Mechanism of action:

Opioids produce their actions at a cellular level by activating opioid receptors. These receptors are distributed throughout the CNS with high concentrations in the nuclei of tractus solitarius, peri-aqueductal grey area (PAG), cerebral cortex, thalamus and the substantia gelatinosa (SG) of the spinal cord. They have also been found on peripheral afferent nerve terminals and many other organs.

Opioid receptors are coupled with inhibitory G-proteins and their activation has a number of actions including: closing of voltage sensitive calcium channels; stimulation of potassium efflux leading to hyperpolarization and reduced cyclic adenosine monophosphate production. Overall, the effect is a reduction in neuronal cell excitability that in turn results in reduced transmission of nociceptive impulses.

Classification of opioid analgesics:

Several classifications have been proposed

- **Traditional:** based upon analgesic potency.
- **Origin of drug:** naturally occurring or synthetic.
- **Function:** their action at the opioid receptor.

1- Morphine

Pharmacological effects:

1-CNS:

a. Analgesia

Continuous dull pain is relieved more effectively than sharp intermittent pain. However, increasing the dose of morphine can control severe intermittent pain as in renal colic.

Mechanism of analgesia:

1- Inhibition of the ascending transmission of nociceptive (painful) information from spinal cord to brain and activation of the analgesic descending circuit from the midbrain to the spinal cord dorsal horn.
The net result is elevation of the pain threshold and reduction of pain perception.

2- Opioids like morphine modify the emotional reaction to pain.

In therapeutic doses, the analgesic effect of morphine is usually associated with drowsiness but no loss of consciousness or motor activity.

b. Sedation:

- Drowsiness, feeling of heaviness and difficulty in concentrating are common.
- Sleep may occur with relief of pain, although they are not true hypnotics.

c. Euphoria and dysphoria:

- Morphine and other opioids cause a sense of contentment and well-being (euphoria).
- If there is no pain, morphine may cause restlessness and agitation (dysphoria).

d. Hallucinations:

- These are more common with KOP agonists such as pentazocine, but morphine and Other MOP agonists as pethidine, diamorphine and fentanyl may also cause hallucinations.

e. Tolerance and dependence:

• Tolerance is the decrease in effect seen despite maintaining a given concentration of a drug. The mechanism is not fully understood but could involve down regulation of opioid receptors.

• Dependence exists when the sudden withdrawn of an opioid, after repeated use over a prolonged period, results in various physical and psychological signs. These include; restlessness, irritability, increased salivation, lacrimation and sweating, muscle cramps, vomiting and diarrhea.

2-Pupil:

- MOP and KOP receptors in Edinger-Westphal nucleus of oculomotor nerve are stimulated by morphine resulting in constriction of the pupils (miosis) and in acute morphine poisoning, pupil becomes pin point. This effect can be reversed by atropine. In addicts, constricted pupil continues.
- Morphine lower IOP in glaucomatous eyes.

2- Respiratory system:

Morphine has a depressant effect on respiratory system through the following:

1. Inhibition of respiratory center.
2. Release of histamine
3. Dryness of bronchial secretion.
4. Depression of cough (through inhibition of cough center).

- Thus, morphine administration as an analgesic is dangerous in patients with bronchial asthma.

- Also, Concurrent use of other CNS depressants, for example benzodiazepines or halogenated anaesthetic, may cause marked respiratory depression.

4- Nausea and vomiting:

Morphine directly stimulates the (CTZ) in the medulla.

5- Cardiovascular system:

a. Morphine in therapeutic dose produces peripheral vasodilatation that may lead to hypotension and fainting. Release of histamine by morphine helps occurrence of peripheral vasodilatation.
b. This vasodilator effect may be blocked partially by histamine H1-receptor antagonist drugs but it is effectively reversed by pure morphine antagonists like naloxone.
c. Morphine may have a cardio-protective effect on ischemic heart (as in angina pectoris and acute myocardial infarction) as it may decrease cardiac preload, rate and contractility (direct effect on the sino-atrial (SA) node), in the way that reduces oxygen consumption. This effect is not observed in normal heart subjects.

6- GIT & biliary tract:

a. Morphine reduces the gastric motility so that passage of gastric content into duodenum is delayed.
b. It also decreases the propulsive peristaltic movement of intestinal tract.
c. Contracts sphincters.
This leads to severe constipation and may leads to intestinal obstruction.
d. Morphine causes spasm of the sphincter of oddi of biliary tract. So, it is not used as an analgesic to treat biliary colic.
Naloxone relieves the spasm effectively.

7- Urinary system and uterus:

a. Morphine may cause urinary retention through inhibition of the urinary reflex and increase the tone of external sphincter so that urinary catheterization may be required with therapeutic dose of morphine.

b. If uterus has been made active by oxytocics, morphine restores it again to normal.

8- Effects on pregnancy and neonates:

• All opioids cross the placenta and if given during labour, can cause neonatal respiratory depression.
• Chronic use by the mother may cause physical dependence in utero and lead to a withdrawal reaction in the neonate at birth that can be life threatening.

9- Histamine release and itching:

• Some opioids cause histamine release from mast cells resulting in urticaria, itching, bronchospasm and hypotension.

• The mechanism is centrally mediated and may be reversed by naloxone.

10- Immune system:

Morphine may exert an immunosuppression. This action has a clinical implication when treating severe pain in immunocompromised patients.
This may explain the susceptibility of infection in morphine addicts (e.g. AIDS and T.B. infection).

Pharmacokinetics:

Absorption:
Morphine is readily absorbed from the GIT if given orally. However, it has an extensive first pass effect that reduces its bioavailability. So, it usually given SC, I.M., or I.V.

Distribution:
About one third of morphine in plasma is bound to plasma protein. Although it enters readily all body tissues including the fetus in pregnant mothers, it crosses the BBB only in a small amount as it is the least lipophilic of other opioids like heroin, fentanyl and methadone.

Metabolism:
Morphine is extensively metabolized by the gut wall and the liver to morphine-3-glucuronide (M3G) (70%), morphine-6 glucuronide (M6G) (10%) and to sulphate conjugates. M6G is 10-20 times more potent than morphine and is normally excreted in urine.

Therapeutic uses:

1- Relief of pain:
Morphine as a strong opioid works best against visceral, somatic and dull continuous pain like cancer pain.
In acute pain, it is usually given I.V.
Biliary colic can not to be treated with morphine as the drug causes spasm of sphincter of Oddi causing increase of intrabiliary pressure.

2- Acute left ventricular failure:
Its peripheral vasodilator effect reduces preload (venodilatation) and afterload (arterial dilatation) of the heart.

3- Preanesthetic medication:
Morphine calms the patient, reduces anesthetic requirement and minimizes the hemodynamic changes produced by painful stimuli.

Adverse effects:

1- Respiratory depression especially in patients with impaired respiratory dysfunction.
2- Nausea and vomiting. Therefore, an antiemetic is preferred to be co-prescribed routinely with opioids for the first 10 days.
3- Constipation: long-term use of opioids like morphine may need to add a stool softner and a laxative to the patient.
4- Smooth muscle spasm: Morphine causes spasm of the sphincter of oddi (causing biliary colic) and the urinary sphincter (causing urinary retention). Thus in biliary or renal colic, another opioid is preferred other than morphine (usually meperidine).
5- Sedation: It is usually mild.
6- Tolerance: Chronic treatment with morphine causes tolerance to its analgesic effect. Consequently, the analgesic dose should be increased, or another opioid analgesic can be substituted, as cross tolerance is not usually complete.
7- Physical dependence (addiction).

Acute morphine poisoning:

It is due to administration of over-dosage (accidental or suicidal).

Manifestations:

1. Coma
2. Pin point pupil
3. Respiratory depression.

Treatment:

IV administration of Naloxone or naltrexone. They are a pure competitive antagonist of morphine.

Precautions during the use of morphine as analgesic:

1- Asthmatic patients.
2- At the onset of labor, if morphine is given to relieve pain, it crosses placenta to fetus causing respiratory center depression (asphyxia neonatorum).
3- Old people and infants are more susceptible to respiratory depression by morphine.
4- In head injuries. Morphine produces miosis and mental disturbances that interfere with diagnosis. Also, morphine-induced respiration causes CO2 retention and cerebral vasodilatation. This can increase the intracranial pressure.
4- In acute abdomen, morphine masks the pain interfering with diagnosis.

2- Codeine

- It is a weak opioid i.e. it is recommended for pain that is not responsive to non-opioid analgesics.
- Metabolized by CYP2D6 (demethylation) forming morphine.
- Genetic polymorphism in the enzyme can lead to the inability to convert codeine to morphine, thus making codeine ineffective as an analgesic in 10% of the Caucasian populations.

- It is a powerful cough suppressant and very constipating.
- It is usually combined with aspirin-like drugs to produce an additive analgesic effect.

3. Diamorphine (heroin)

- A semi-synthetic opioid, the diacetylated analogue of morphine. It is 1.5-2.0 times more potent than morphine. It is a pro-drug and is converted to the active components of acetylmorphine and morphine.

Pharmacokinetics

- Diamorphine is 200 times more lipid soluble than morphine and, therefore, passes more rapidly across the blood-brain barrier into the CNS where it is converted to morphine. Therefore, it has more analgesic potency and a more rapid onset of action than morphine.

Effects

- It shares common opioid effects with morphine. It is associated with an increased tendency to cause euphoria and dependency. • May cause less nausea and vomiting than morphine.

4- Tramadol

- Codeine like analogue with weak μ-agonist activity.
- It is a monoamine (norepinephrine and serotonin) reuptake inhibitor.
- It is effective in mild to moderate pain.
- In acute and severe pain, its effect is limited by increased risk of tramadol-induced nausea and vomiting.
- Its mono-aminergic activity (antidepressant) may share in its ability to control neuropathic pain.
- The mood-elevating property (euphoria effect) related to the drug is related to its monoaminergic activity.
- It should not also be given with MAO inhibitors because of its effect on serotonin-reuptake.
- Physical dependence and severe withdrawal manifestations have been reported with the drug.
- In therapeutic dose, it has Iess respiratory depressant, or constipating effect. However, it may induce seizure. So given cautiously in epileptic patients.

5-Meperidine

It is a synthetic opioid like drug.
It is about 1/10 as potent as morphine for pain relief.

Like morphine, meperidine may produce:

1. Sedation.
2. Euphoria.

3. Respiratory depression.
4. Miosis.

Unlike morphine, meperidine

1. Does not suppress cough reflex.
2. Non constipating.
3. No urinary retention.
4. It has a shorter duration of action than morphine (2-4 hours)
5. In large doses it produces dilatation of the pupil (atropine like action)
6. It is metabolized to normeperidine in the liver (N-demethylation) which on accumulation may produce an excitatory CNS effect and convulsions.

Therapeutic uses:

1- Acute pain, but not suitable for chronic pain for fear of convulsive potential of its metabolite normeperidine.
3- Obstetric analgesia as it does not depress uterine contraction in labor.

6-Fentanyl

100 times more potent as analgesic than morphine. It is usually given I.V. or intrathecally. But transdermal patches are also available for sustained release analgesic effect.
It is used as an anesthetic adjuvant to relieve pain postoperatively, during labor and in control of chronic pain of malignant or non-malignant cause.
As it has negligible effect on cardiac contractility, so it is often used in cardiac surgery.
Its congener sufentanil has a similar effect with 1000 times more potent than morphine in analgesia.

7-Diphenoxylate and Loperamide

They are meperidine analogs
They have opioid like action on the GIT (constipating effect)
At the usual doses, they lack opioid analgesic effect but have antidiarrheal effect.
Adverse effects: abdominal cramps.

8-Methadone

It is equal in potency to morphine.

Unlike morphine, methadone:

1. Well absorbed orally.
2. Longer duration of action.
3. Less euphoric effect.
4. It is used in treatment of morphine addicts as it produces similar effects and, on its withdrawal, the symptoms of its withdrawal are milder than with morphine.

9-Buprenorphine

It is a partial agonist at μ-opioid receptor.
Buprenorphine has been recently approved by FDA in treatment of morphine addiction.
It may be combined with methadone.

10- Naloxone and naltrexone

They are pure antagonist to opioid receptors especially for μ-opioid receptor.

Therapeutic uses:

1. Acute opioid poisoning,
2. Opioid-induced fetal (neonatal) asphyxia,
3. Diagnosis of opioid addict (their administration induce withdrawal symptoms).

Naloxone has extensive hepatic metabolism, so it is given IV. Its duration of action is 1-4 hours (short duration).

Naltrexone has high oral efficacy and can be given orally.
It is more potent than naloxone and has longer duration of action (about 24 hours).

Antiepileptic drugs

Definition:

- Epilepsy is a Chronic medical condition produced by sudden changes in the electrical function of the brain.
- The characteristic event is the seizure, which is often associated with convulsion, but may occur in many other forms.
- The seizure is caused by an abnormal high frequency discharge of a group of neurons, starting locally and spreading to a varying extent to affect other parts of the brain.

Etiology:

1. **Idiopathic:** the most common.
2. **Secondary:**

a. Head injuries, trauma, depressed skull fractures.
b. Infection e.g. meningitis, brain abscess, viral encephalitis.
c. Brain tumors.
d. vascular disorders.
e. Drug withdrawal, e.g. CNS depressants.
f. Fever in children (febrile convulsion).

Types of epilepsy:

1- Generalized seizures:

Involve the whole brain, including the reticular system, thus producing abnormal electrical activity throughout both hemispheres. The seizures are associated with impairment of consciousness.

They include the following subtypes:

a) Tonic-clonic convulsions (grand mal):

It is the most common. Without warning, the patient suddenly loses consciousness, with rigidity and, arrest of respiration lasting less than 1 minute (tonic phase), followed by clonic phase where jerking movement of body muscles occurs.

Other associated features may include tongue biting, incontinence, and salivation. After few minutes, convulsions stop and the patients become drowsy, exhausted, and may enter into sleep.

b) Absence seizures (petit mal):

They are common in childhood and early adolescence and usually stop by age of 20. The seizure comes as a brief, sudden and self-limiting loss of consciousness. The child stares and exerts rapid eye blinking.

The attack lasts for few seconds and may be associated with loss of postural tone or autonomic symptoms like enuresis. The patient often unaware of attacks.

c) Myoclonic seizures:

Single or multiple myoclonic jerks presented as abrupt and very brief short attacks of involuntary muscle contractions usually after wakening in the morning and affect the limbs, head or sometimes the whole body.

2- Partial seizures:

The discharge begins locally, and often remains localized. Produce relatively simple symptoms without loss of consciousness.

They include the following subtypes:

a) Simple partial seizure:

Consciousness is preserved. The electrical discharge is confined to the motor area and may take a motor style like convulsions in a single limb or a group of muscles, or sensory area and take sensory style such as numbness or abnormal sensation or even autonomic style such as abnormal epigastric sensations or papillary dilatation.

b) Complete partial (psychomotor):

They usually originate in temporal or frontal lobes of the brain. They are associated with impaired consciousness, psychic symptoms like sensory hallucinations and altered behavior like pulling of his clothes.

3- Status epilepticus:

It is an emergency condition where seizures are repeated without recovery between them. The epileptic status may last 30 minutes.

Mechanisms of action of antiepileptic drugs:

1. Blockade of voltage-gated ion channels (Na+ and Ca2+) which affect neuronal discharge and action potential.
2. Enhancement of the inhibitory GABAergic neurotranmission.
3. Interference with excitatory glutamate neurotransmission.

Classifications of antiepileptic drugs:

1- Old (first generation) and new (second generation):

Old (first generation)

e.g. phenytoin, carbamazepine, phenobarbital, ethosuximide, valproic acid, and benzodiazepines

New (second generation)

e.g. lamotrigine, topiramate, oxcarbazepine, levetiracetam, gabapentin, felbamate, and tiagabine.

2- According to the type of epilepsy:

a. Generalized tonic clonic (grand mal) or partial seizures

Old: phenytoin, carbamazepine, valproic acid, phenobarbital, primidone,

New: lamotrigine, topiramate, oxcarbazepine, levetiracetam, zonisamide, tiagabine, felbamate and gabapentine.

b. Absence (petit mal) seizures

Valproic acid, ethosuximide, and clonazepam.

c. Myoclonic jerks

Valproic acid and clonazepam.

I- Old (first generation)

1- Phenytoin

It is a traditional first generation.

Mechanism of action:

It has a sodium channel blocking activity.

Pharmacokinetics:

1. Highly plasma protein binding (90%) and can displace other drugs from protein binding (possible drug-drug interaction)
2. Metabolized in the liver by hydroxylation (CYP 450) followed by glucuronidation. It is liver microsomal enzyme inducer (accelerates its own metabolism and metabolism of other drugs concomitantly given).
3. It elimination follows zero-order (saturation) kinetic. So, small increase of the daily dose may cause marked increase in its plasma concentration and developed drug toxicity.
4. It has a narrow therapeutic index (therapeutic range: 10-20 ug/ml) which necessitates therapeutic drug monitoring to avoid toxicity if dose is increased.
5. Oral preparations of phenytoin may have different bioavailability. So, patients stabilized on one formulation should continue to receive the same formulation.

Therapeutic uses:

Grand mal and partial seizure.

I.V. in status epilepticus. Fosphenytoin is a prodrug that is rapidly converted into phenytoin in the blood.

Antiarrhythmic in ventricular dysrhythmia and digitalis induced supraventricular dysrhythmia (phenytoin has a sodium channel blocking activity).

Adverse effects:

10% of patients may withdraw the drug because of its side effects on prolonged use. They are usually dose related and may include:

Skin rash, gum hyperplasia, hirsutism and acne.

Folate deficiency and osteomalacia.

Nystagmus, vertigo, ataxia and diplopia.

Rarely, blood dyscrasias and hepatic failure.

2- Carbamazepine:

Mechanism of action:

As phenytoin, carbamazepine has a sodium channel blocking activity.

Pharmacokinetics:

1. It is metabolized in the liver mainly by CYP3A4 and changes into an active metabolite (10,11epoxide metabolite) which in turn changes into an inactive metabolite that is excreted in urine as glucuronide conjugate.
2. Carbamazepine is a liver microsomal enzyme inducer. It induces its own metabolism (autoinduction) and metabolism of other concomitantly given drugs.
3. The autoinduction character of carbamazepine delays arrival of the drug to its steady state concentration. Therefore, the drug is introduced at low dose and the dose is increased gradually till autoinduction is complete and the drug level stabilizes at a steady state concentration which takes about one month.
4. Carbamazepine is one of the drugs that need follow up of their plasma concentrations (therapeutic drug monitoring). Therapeutic range of its plasma concentration is 4-11 ug/ml.

Therapeutic uses:

Generalized tonic clonic and partial seizures, but not petit-mal epilepsy

Trigeminal neuralgia.

Mood stabilizer in patients with bipolar affective disorders.

Adverse effects:

Skin rash early may occur early in therapy but may not require changing the drug.

Dose-related side effects like drowsiness, vertigo, diplopia, blurred vision and ataxia

Serious: hepatic failure and bone marrow suppression.

3- Valproic acid:

Mechanism of action:

It has a wide spectrum of anti-seizure action including sodium channel blockade, calcium channel blockade and enhancement of GABA-ergic system. All these actions give it a broad-spectrum anti-seizure activity.

Pharmacokinetic:

1. Highly bound to plasma protein (> 90%) which may cause interaction with other highly protein bound drugs.
2. It is metabolized in the liver mainly by glucuronidation and β-oxidation. Some of its metabolites have antiseizure activity.
3. Valproic acid is a liver microsomal enzyme inhibitor. This makes a possibility of drug-drug interactions.
4. Like carbamzepine and phenytoin, velproic acid has a narrow therapeutic range in blood is 50-100 ug/ml.

Therapeutic uses:

Partial and generalized seizures including petit-mal (absence) seizure.

Mood stabilizer in bipolar affective disorder.

Adverse effects:

GIT: anorexia, nausea and vomiting.

CNS: sedation, ataxia and tremor.

Rash, alopecia, increased appetite and gaining weight.
Elevation of liver enzymes, rarely hepatitis and pancreatitis.

4- Phenobarbital:

It is a long-acting barbiturates with broad spectrum anticonvulsant activity. However, its adverse effects on cognitive function and possibility of development of tolerance to its effect.

Mechanism of action:

Increases the inhibitory effect of GABA-ergic system and inhibition of the excitatory effect of glutamate.

Pharmacokinetics:

It is a liver microsomal enzyme inducer that allows interaction with other drugs. 25% of the drug is eliminated unchanged by the kidney while the remaining part is metabolized in the liver. Decreased elimination is expected in hepatic or renal impairment.

Therapeutic uses:

Phenobarbital is given I.V. in status epilepticus and as an alternative chronic therapy in cases of refractory epilepsy to other medication.

Adverse effects:

Sedation, cognitive impairment, osteoporosis, tolerance and physical dependence.

Primidone

It is another antiepileptic drug that principally metabolized into Phenobarbital with similar effects and side effects like Phenobarbital.

5- Ethosuximide:

It is specific in treatment of generalized absence seizure only.

Mechanism of action:

It acts specifically on T-type calcium channels in the brain reducing propagation of abnormal electrical activity.

Pharmacokinetics:

Its half-life is between 30-50 hours. So, it is cumulative and increase in daily dose may lead to higher increases in average plasma concentrations. Therefore, careful monitoring of its plasma concentration is indicated at high doses.

Adverse effects:

Gastrointestinal disordres at the beginning of therapy, but also headache, fatigue and sleep disturbance may occur.

6- Benzodiazepines:

It acts on GABA-A receptors.

Diazepam: it is given rectal or IV mainly for status epilepticus and febrile Seizures.

Clonazepam: specific for absence seizures

II- New (second generation)

- Relatively lack of drug-drug interaction (simple pharmacokinetic profile) and improved tolerability.
- They are usually considered as second line antiepileptic drugs (with some exceptions) and to be used as add on therapy when first line (old or first generation) drugs fail to control the disease.
- They all are approved as add on (adjunctive) therapy to other anti- seizure drugs for partial seizures.

1- Gabapentin

It is GABA analogue but does not act on GABA receptors or enhance GABA action. Its exact mechanism of action is unknown.

Excreted unchanged by the kidney and dose should be modified with renal impairment.

Therapeutic uses:

As an adjunct with other anti-epileptics in tonic-clonic, clonic, and partial seizures.

Also used in migraine, and chronic pain.

2- Lamotrigine

Mechanism of action:

It inhibits synaptic release of excitatory glutamate through sodium channel blocking activity.

Pharmacokinetics:

- It is metabolized in the liver by glucuronidation.
- It does not induce or inhibit C. P-450 isozymes (its metabolism is inhibited by valproate) .

Therapeutic uses:

As an adjunct therapy or as monotherapy in tonic-clonic, absence and partial seizures.

3- Levetiracetam

It binds to a brain protein called synaptic vesicle protein SVZA where it mediates its anti-seizure activity.

4- Oxcarbazepine

It is an analogue of carbamazepine.

It is an inactive pro-drug that is converted in the liver into active metabolite 10 hydroxy metabolite.

It has similar efficacy to carbamazepine but it does not induce liver enzymes and used in patients allergic to carbamazepine.

5- Topiramate

Mechanism of action:

It has several mechanisms of anti-seizure activity including inhibitory effects on sodium channel, calcium channel, carbonic anhydrase enzyme and NMDA at glutamate site, and stimulatory effect on GABA receptors increasing the chloride channel conductance activity.

Pharmacokinetics:

Excreted mainly unchanged by the kidney. It reduces plasma concentration of estradiol, so dose of concomitantly given oral contraceptives should be increased.

Therapeutic uses:

Recently, this drug becomes one of the safest anti-epileptics which can be used alone for partial and generalized tonic-clonic seizures.

Adverse effects:

Renal calculi due to inhibition of carbonic anhydrase.

6- Felbamate

It has multiple mechanisms as anti-seizure including sodium channel, calcium channel blocking activity, compete with glycine on NMDA glutamate receptors, and potentiate GABA action.

Because of the risk of aplastic anemia and hepatic failure during its use, it is limited for cases of refractory epilepsies and not to be used as a first line drug. When used, blood counts should be performed monthly.

Endocrine Pharmacology

1. Glucocorticoids

Glucocorticoids are steroid hormones which have important effects on carbohydrate, fat and protein metabolism, catabolism, immune responses, and inflammation and include cortisone and cortisol.

Mechanism of action of Glucocorticoids:

In response to glucocorticoids binding, the glucocorticoid receptors dissociate from their bound proteins and move into the nucleus where they interact with glucocorticoid response elements (GREs) for the specific gene transcription by glucocorticoids.

Pharmacological effects:

1-Metabolic effects:

1. Carbohydrate metabolism:

- Anti-insulin effect: stimulate gluconeogenesis and inhibit glucose uptake and utilization by tissues.
- Stimulate synthesis of glycogen from pyruvate (glycogenesis) in the liver, and prevent glucose output from the liver.
- The net result is Hyperglycemia and glucosuria (glucose intolerance).

2. Protein metabolism:

- Glucocorticoids cause protein catabolism in most tissues leading to muscle wasting and myopathy, osteoporosis, growth retardation in children, and delayed wound healing.

3. Fat metabolism:

- Glucocorticoids cause redistribution of body fat such as in Cushing's syndrome. There is increased fat in the back of the neck (buffalo hump), face (moon face). This is known as fat redistribution.

4. Ca^{2+} metabolism:

- Glucocorticoids have anti-vitamin D action and accordingly decrease Ca^{2+} absorption from GIT, leading to hypocalcemia.

2. Mineralocorticoid action:

Glucocorticoids have aldosterone-like action causing Na+ and water reabsorption and hypokalemia. This may lead to edema and elevation of blood pressure.

3. Action on CVS:

Glucocorticoids increase blood pressure by the following mechanisms:

1. Sodium and water retention by its mineralocorticoid action which increases cardiac output.

2. Enhancement of the vasoconstrictor action of noradrenaline and angiotensin II, which increases total peripheral resistance.

3. Decrease in capillary permeability thus maintaining blood volume.

4. Action on respiratory system:

- Anti-inflammatory and stabilization of the membrane of mast cells to prevent the release of allergic mediators in bronchial asthma.
- Increase number of β2-receptors and prevents down regulation by β2-agonists as salbutamol.

- Stimulate production of surfactant in neonates.

5. Action on CNS:

Corticosteroids elevate the mood and give a sense of well-being. They maintain blood pressure, plasma glucose concentrations and electrolyte concentrations.

6. Action on GIT:

Corticosteroids inhibit synthesis of cytoprotective PGE2 and PGI2. So, increase HCl and decrease mucus leading to peptic ulcer.

7. Skeletal muscle:

- Corticosteroids in normal concentrations of are required for the normal function of skeletal muscle.
- In Addison's disease, muscle weakness and easy fatigability develop.

8. Anti-inflammatory effect:

1. By inhibition of both phospholipase A2 and cyclooxygenases.

2. Inhibit migration of neutrophils.

3. Decrease circulating lymphocytes, eosinophils, monocytes, basophils.

4. Decrease synthesis of inflammatory cytokines as interleukins, TNFα, and colony stimulating factor (CSF).

5. Stabilize lysosomal membrane and inhibit release of lysosomal enzymes thus preventing cell death and tissue destruction.

6. Decrease capillary permeability thus decreasing inflammatory edema and joint effusion.

9. Immunosuppressive and Anti-allergic effects:

By inhibition of antibody (immunoglobulins) formation, inhibition of antigen-antibody reaction and decrease tissue response to inflammatory mediators.

Therapeutic uses:

1. Replacement therapy in the following conditions: adrenal insufficiency, either primary (Addison's disease) or secondary, acute or chronic.

2. Anti-inflammatory and immunosuppressive in auto-immune diseases such as rheumatic carditis, osteoarthritis or tendinitis.

3. Bronchial asthma: inhaled steroids as beclomethasone in prophylaxis, and hydrocortisone sodium succinate I.V. in status asthmaticus.

4. Renal diseases: such as nephritic syndrome.

5. Infectious diseases: like AIDS patients with pneumocystis, hemophilus influenza type B, meningitis and septic shock.

6. Anti-allergic in angioneurotic edema, dermatitis, allergic rhinitis, allergic conjunctivitis, anaphylactic shock. Skin diseases: eczema and psoriasis.

7. Gastrointestinal diseases: like inflammatory bowel disease (chronic ulcerative colitis).

8. Cerebral edema.

9. Blood diseases as: leukemia (acute lymphocytic leukemia), thrombocytopenic purpura, agranulocytosis, and hemolytic anemia.

10. Immunosuppressive after organ transplantation to prevent rejection.

11. Malignancies: acute leukemia and lymphomas.

12. Acceleration of lung maturation: respiratory distress syndrome is a problem in premature infants. Fetal cortisol is a regulator of lung maturation. Consequently, a dose of betamethasone or dexamethasone is administered intramuscularly to the pregnant women in premature labor to hasten maturation of the fetal lungs.

Adverse effects and toxicity:

1- Secondary to sudden withdrawal of therapy:

- Acute adrenal insufficiency: if steroid withdrawal is rapid after prolonged therapy (e.g. 2-4 weeks or more).
- Withdrawal symptoms include fever, myalgia, arthralgia, and malaise.

2- Secondary to continued use:

1. Edema, hypertension and hypokalemic alkalosis.
2. Metabolic changes: hyperglycemia with glycosuria.
3. Increased susceptibility to infection and a risk for reactivation of latent tuberculosis.
4. Peptic ulcer.
5. Myopathy: It is characterized by weakness.
6. Behavioral changes: nervousness, insomnia and euphoria.
7. Eye: glaucoma.
8. Osteoporosis.
9. Growth retardation in children.
10. Cushing'features: moon face, buffalo hump, enlarged supraclavicular fat, central obesity, hirsutism and acne.
11. Repeated intra-articular injections lead to painless joint destruction.
12. Delay of wound healing after surgery.

Contraindications:

1. Absolute:

Herpes simplex keratitis.

It is a viral infection of the eye that can be increased in the presence of corticosteroids leading to irreversible clouding of the cornea. Also, topical steroids should not be used in treating mechanical lacerations of the eye as they delay healing and promote spread of infection.

2. Relative:

Hypertension, diabetes mellitus, peptic ulcer, osteoporosis, psychotic tendency, acute or chronic infections.

Important members of glucocorticoids:

1. Cortisol:

- The major natural glucocorticoid is cortisol.

- The physiologic secretion of cortisol is regulated by adrenocorticotropin (ACTH) and varies during the day (circadian rhythm); the peak occurs in the morning and the trough occurs about midnight.
- When given orally, cortisol is well absorbed from the GIT tract, it is cleared by the liver, and has a short duration of action compared with its synthetic congeners.

- Although it diffuses poorly across normal skin, cortisol is readily absorbed across inflamed skin and mucous membranes.

2. Synthetic glucocorticoids:

- The mechanism of action of these agents is identical with that of cortisol.

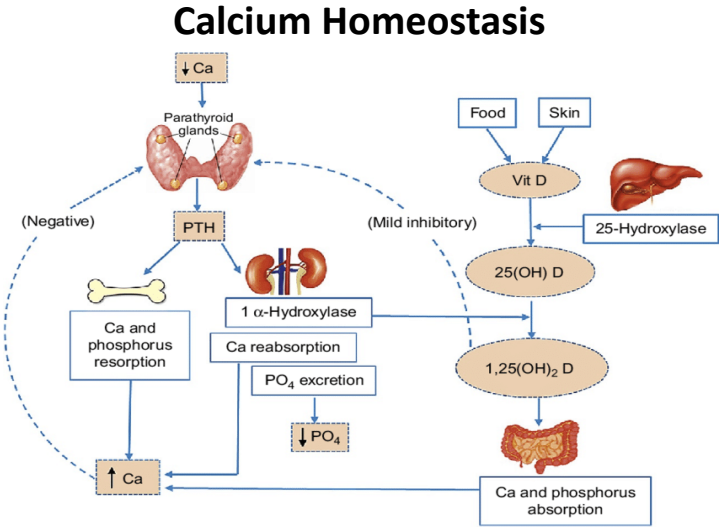
- A large number of synthetic glucocorticoids are available for use; prednisone and its active metabolite, prednisolone, dexamethasone, and triamcinolone.

- Their properties (compared with cortisol) include longer half-life and duration of action, and better penetration of lipid barriers for topical activity.

- Special glucocorticoids have been developed for use in asthma such as beclomethasone and budesonide readily penetrate the airway mucosa but have very short half-lives after they enter the blood, so that systemic effects and toxicity are greatly reduced.

2. Calcium Homeostasis

Normal range of serum calcium (Ca2+) is 9-11 mg/dL by the action of parathyroid hormone (parathormone), calcitonin, and vitamin D mainly and to a less extent by the effect of glucocorticoids and estrogen. Some and drugs as thiazide and loop diuretics may affect serum calcium.



Factors Affecting Calcium Homeostasis:

1. Parathormone:

Mechanism of action:

- Activation of Gs coupled membrane receptors and increase c-AMP in bone and renal tubular cells. This leads to increased serum Ca2+ and decreased phosphate.

- In the kidney, PTH inhibits calcium excretion, promotes phosphate excretion, and stimulates the production of active vitamin D metabolites.

- In bone, PTH promotes bone turnover by increasing the activity of both osteoblasts and osteoclasts.

Therapeutic uses:

1. Treatment of hypoparathyroidism causing hypocalcemia and tetany.

2. Intermittent use of small doses stimulates bone growth in osteoporosis.

Teriparatide: is a recombinant PTH used parenterally for the treatment of osteoporosis.

2. Calcitonin:

Mechanism of action:

Calcitonin, a peptide hormone secreted by the thyroid gland, decreases serum calcium and phosphate by inhibiting bone resorption and inhibiting renal reabsorption of these minerals.

Therapeutic uses:

1. Treatment of hypercalcemia.

2. Paget's disease of bone.

3. Calcitonin is approved for treatment of osteoporosis and has been shown to increase bone mass and to reduce spine fractures. However, it is not as effective as teriparatide or bisphosphonates.

3. Vitamin D:

- Vitamin D, a fat-soluble vitamin, it can be synthesized in the skin from 7-dehydrocholesterol under the influence of ultraviolet light or absorbed from the diet in the natural form (vitamin D3, cholecalciferol) or the plant form (vitamin D2, ergocalciferol).

- Active metabolites are formed in the liver (25-hydroxyvitamin D or calcifediol) and kidney (1, 25-dihydroxyvitamin D or calcitriol plus other metabolites).

- Renal synthesis of active vitamin D metabolites is stimulated by PTH.
- Synthesis of 1, 25-dihydroxyvitamin D2 is inhibited by phosphate, fibroblast growth factor 23 (FGF23).

Mechanism of action:

It increases serum concentrations of calcium and phosphate by increasing intestinal absorption and bone resorption and decreasing renal excretion.

Therapeutic uses:

1. Hypocalcemia caused by nutritional deficiency, intestinal osteodystrophy, chronic kidney or liver disease, hypoparathyroidism, and nephrotic syndrome.

2. Rickets and osteomalacia.

3. Post-menauposal osteoporosis with dietary Ca2+.

Other Factors Affecting Calcium Homeostasis:

1. **Bisphosphonates:**

They inhibit bone resorption. They are used in treatment of osteoporosis, Paget's disease and hypercalcemia associated with malignancy.

Examples: **alendronate**, **etidronate**, **pamidronate**, and **risedronate**.

2. **Estrogens and SERM as Raloxifen**:

They inhibit parathormone-induced bone resorption in menopause, used it treatment and prophylaxis of postmenopausal osteoporosis.

3. Thiazide diuretics: decrease Ca2+ excretion in urine and cause hypercalcemia, used in hypocalcemia and idiopathic hypercalciuria.

4. Loop diuretics: decrease blood Ca2+ and are used in hypercalcemia.

5. Glucocorticoids: antagonize vitamin D and decrease Ca2+ absorption from GIT leading to hypocalcemia, and are used in hypercalcemia.

6. Fluoride: it increases bone Ca2+ deposition and prevents dental caries, and is used in postmenopausal osteoporosis.

Treatment of Osteoporosis:

Osteoporosis occurs in post-menopausal females- due to long treatment with glucocorticoids, hyperparathyroidism, thyrotoxicosis, and alcoholism.

Treatment includes:

1. Ca+ and vitamin D.

2. Bisphosphonates.

3. Estrogen and Raloxifen (better than estrogen to reduce the risk of breast and endometrial carcinoma).

4. Calcitonin.

5. Fluoride sustained release.

6. Teriparatide: recombinant parathormone given in small pulse doses.

Treatment of Hypocalcemia:

1. Ca2+ and vitamin D.

2. Parathormone.

3. Thiazides.

Treatment of Hypercalcemia:

1. Biphosphonates.

2. Mithramycin.

3. Calcitonin and phosphate.

4. Glucocorticoids.

5. Ca2+-chelating agents as disodium edetate IV.
6. Phosphate.

Treatment of hypoparathyroidism:

Hypoparathyroidism is either idiopathic or following thyroidectomy.

It is characterized by low serum calcium and high phosphate leading to tetany.

Treatment by:

1. Parathormone.

2. Calcium gluconate slowly IV.

3. Vitamin D.