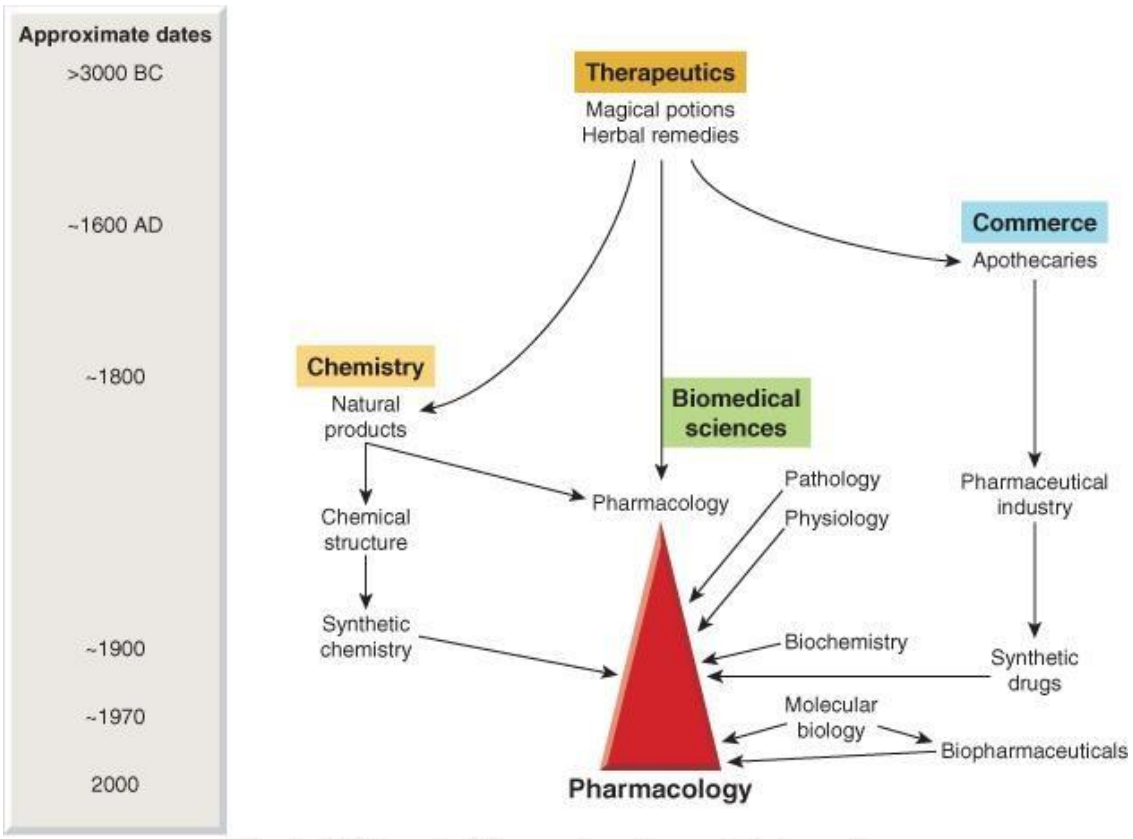
Week	Theoretical subject	Practical
1	General aspects of Drugs Parmacology – Dose –Routes of Administration – Name and classification	Routes of administration Drugs
2	Pharmacodynamics -Drugs-receptors	Discusstion
3	Pharmacokinetics -–Absorption – Distribution –Metabolism-Excretion	Seminar
4	Drugs , Autonomic –N S - Neurotransmitters ,receptors	Absorption ,Excreation (Iodines ,Salicylates)
5	Cholinergic drugs Anticholinergic drugs , Ganglionic blocking drugs Neuromuscular blocking drugs	Discusstion
6	Adrenergic drugs Adrenergic α ,β blocking drugs	Seminar
7	C N S Depressant : Alcohol - Sedative hypnotics Benzodiazepine Barbiturate, Anticonvulsant,Antidepressant	Drugs antagonism Morphine and Nalorphine Curare –Physostigmine
8	C N S Stimulant drugs.	Discusstion
9	Anlgesic : Narcotin or Opioid -NSAIDs	Seminar
10	Anesthetics , General ,Local	Effect of parasympathetic drugs on glandular secreation
11	Drugs act on Respiratory system Bronchodilators ,Expectorants Anti-tussive ,Cold prepration	Discusstion
12	Drugs act on GIT , Anti ulcer Antaacid Antidiarrheal , Anti-emetic ,Laxative	Seminar
13	Diuretics ,classification ,mode of action	Evaution of analgesics
14	Cardio Vascular Drugs-Cardiac Glycosides ,Vasodilators-Antianginal ,Antiarrhrthmic drugs	Discusstion
15	Antihypertensive drugs ,-Drugs affect heamostasis ,Anticoagulant	Seminar

THE HISTORY OF PHARMACOLOGY:

Prehistoric people recognized the beneficial or toxic effects of many plant and animal materials. Early written records from Iraq, China and from Egypt list remedies, including a few still recognized as useful drugs today. however, were worthless or actually harmful .

In the 1500 years ago introduced rational methods into medicine, but none was successful owing to the dominance of systems of thought that purported to explain all of biology and disease without the need for experimentation and observation, This idea disease was caused by excesses of bile or blood in the body, that wounds could be healed by applying a saliva to the weapon that caused the wound. Around the end of the 17th century, reliance on observation and experimentation began to replace theorizing in medicine. As the value of these methods in the study of disease became clear, physicians began to apply them to the effects of traditional drugs used in their own practices.

In the late 18th and early 19th centuries, began to develop the methods of **experimental animal physiology** and **pharmacology**. Advances in chemistry and the further development of physiology therapeutics ,only about 50 years ago it become possible to evaluate therapeutic claims. Around the same time, a major expansion of research efforts in all areas of biology began. As new concepts and new techniques were introduced, information accumulated about drug action.



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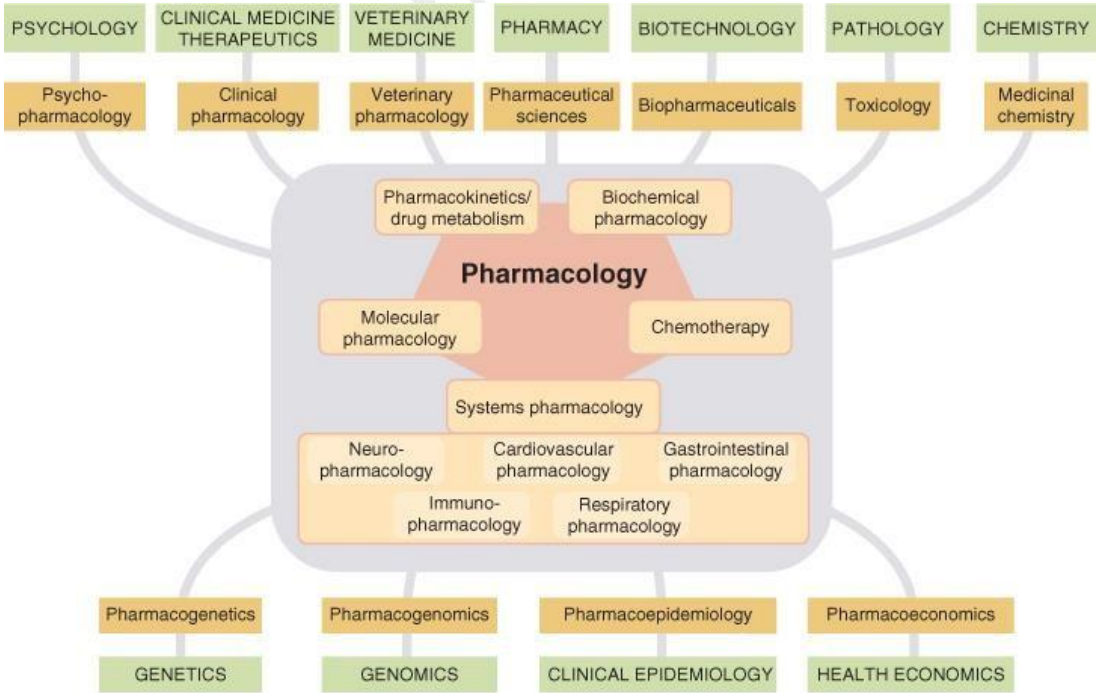

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Two general principles that the student should always remember are, first, that *all* substances can under certain circumstances be toxic; and second, that all dietary supplements and all therapies promoted as health-enhancing should meet the same standards of efficacy and safety,.

Pharmacology

can be defined as the study of substances that interact with living systems through binding to regulatory molecules and activating or inhibiting normal body processes. These substances may be administered to achieve a beneficial therapeutic effect on some process or for their toxic effects on regulatory processes in the patient

Medical pharmacology

defined as the science of substances used to prevent, diagnose, and treat disease.

Toxicology

is that branch of pharmacology which deals with the undesirable effects of chemicals on living systems, from individual cells to complex system

Pharmacogenetics

Which a branch of pharmacology deal with genetic basis for difference drug responsiveness among population

Drug

Drug may be defined as any substance that produce a change in biologic function through its actions. In the great majority of cases, the drug molecule interact with a specific molecule in the biologic system that plays a regulatory role.

This molecules called a **Receptor**. Drugs may be synthesized within the body (e.g., **Hormones**) or may be chemicals *not* synthesized in the body,

Drug to interact chemically with its receptor, a drug molecule must have the **Appropriate size , Electrical charge, Shape, and Atomic composition.**

Furthermore, a drug is often administered at a location distant from its intended site of action, e.g., a pill given orally to relieve a headache. Therefore, a useful drug must have the necessary properties to be transported from its site of administration to its site of action. Finally, a practical drug should be inactivated or excreted from the body at a reasonable rate so that its actions will be of appropriate duration

Drugs may be solid at room temperature (e.g., aspirin, atropine), liquid (e.g., nicotine,), or gaseous (e.g., nitrous oxide). These factors often determine the best route of administration.

Classification of drugs

Drugs may be classified by:

1• Body system, e.g. alimentary, cardiovascular

2• Therapeutic use, receptor blockers, enzyme inhibitors, ion channels

3• Mode or site of action. loop diuretic

4 Molecular structure, e.g. glycoside, alkaloid, steroid

Nomenclature (names) of drugs

Any drug may have names in all three of the following classes:

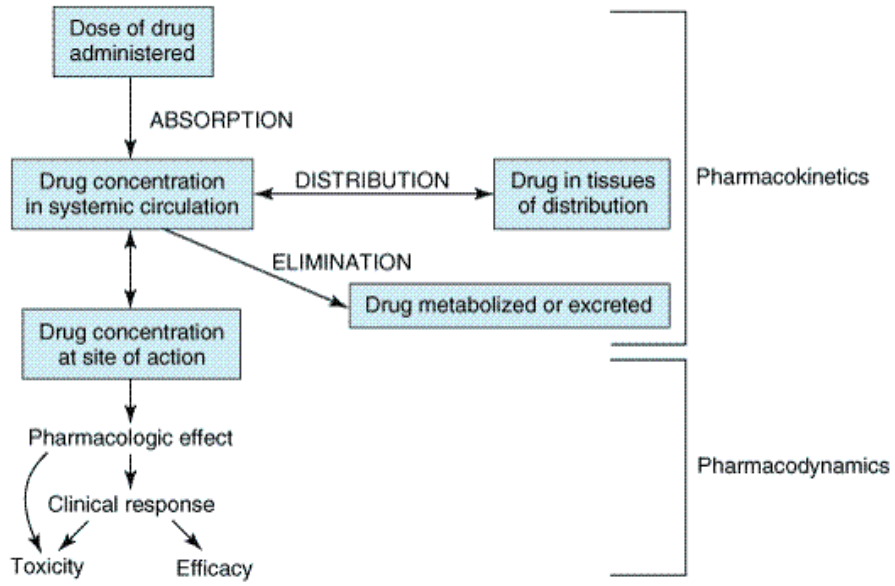
1. The full chemical name

2. A nonproprietary (official, approved, generic) name

3.A *proprietary (brand)* name

Example: one drug — three names

1. 3-(10, 11-dihydro-5H-dibenz [b.*f*]-azepin-5-yl) propyldimethylamine
2. imipramine
3. Tofranil (UK), Prodepress, Surplix, Deprinol, etc (various countries)



Pharmacodynamics

What drugs do to the body(Mechanisms of drug action)

1-Drugs act on the cell membrane by:

A- Action on specific receptors e.g. histamine receptors

B- Interference with selective *passage of ions across membranes,* e.g. calcium entry (or channel) blockers

C- Inhibition of membrane bound enzymes and pumps, e.g. membrane bound ATPase by cardiac glycoside.

2-Drugs act on metabolic processes within the cell

A-*Enzyme inhibition,*

B-Inhibition of *transport processes*.

C- *Incorporation into larger molecules*

D- Altering metabolic processes .

3-Drugs act outside the cell by:

A *Direct chemical interaction,* e.g., antacids

B *Osmosis,* as with purgatives, e.g. magnesium sulphate, and diuretics, e.g. mannitol,.

RECEPTORS

Most receptors are protein macro-molecules. When the natural transmitter or hormone (endogenous ligands) binds to the receptor, the proteins undergo an alteration in conformation which induces changes in systems.

Types of Drug- receptors interaction

1-Agonists. Drugs that activate receptors do so because they resemble the natural transmitter or hormone (endogenous ligands)

2-Antagonists (blockers) of receptors are sufficiently similar to the natural agonist to be 'recognised' by the receptor and to occupy it without activating a response, thereby preventing (blocking) the natural agonist from exerting its effect

3- Partial agonists. Some drugs, in addition to blocking access of the natural agonist to the receptor, are capable of a low degree of activation, i.e. they have both antagonist and agonist action..

4-Inverse agonists. Some substances produce effects that are specifically opposite to those of the agonist.

5-Physiological (functional) antagonism

mechanism by which one drug may oppose the effect of another drugs

ENZYMES

Interaction between drug and enzyme is in many respects similar to that between drug and receptor. Drugs may alter enzyme activity because they resemble a natural substrate and hence compete with it for the enzyme.

POTENCY AND EFFICACY

. **Potency** is the amount (weight) of drug in relation to its effect, e.g. if weight-for-weight drug A has a greater effect than drug B, then drug A is more potent than drug B.

Pharmacological efficacy refers to the strength of response induced by occupancy of a receptor by an agonist.

Therapeutic efficacy effectiveness, is the capacity of a drug to produce an effect and refers to the maximum such effect, e.g. if drug A can produce a therapeutic effect that cannot be obtained with drug B, however much of drug B is given, then drug A has the higher therapeutic efficacy.

TOLERANCE

Continuous or repeated or administration of a drug is often accompanied by a gradual diminution of the effect it produces..

Drug passage across cell membranes

- **1-Passive diffusion**
- **2-Filtration and bulk flow**
- **3-Endocytosis**
- **4-Ion-pairing**
- **5-Active transport**

Pharmacokinetics is what the body does to drugs

The individual processes

(Absorption, Distribution , (Metabolism (biotransformation), Execration) Elimination.

Absorption

Considerations of anatomy, physiology, pathology, pharmacology, therapeutics and convenience determine the routes by which drugs are administered. Usually these are:

1-• *Interal :* by mouth (swallowed) or by sublingual or by rectum

2• *Parenteral:* by injection to intravenous or, intramuscular, subcutaneous or infusion,

3• *Other routes,* e.g. inhalation, topical application for local (skin, eye, lung) or for systemic (trans dermal) effect intrathecal, intradermal, intranasal, intratracheal, intrapleural, are used when appropriate.

Presystemic (first-pass) elimination.

drugs are metabolized in a single passage through the gut wall and (principally) the liver.

ADVANTAGES AND DISADVANTAGES OF ENTERAL ADMINISTRATION

Swallowing

-Advantages are convenience , acceptability and economic

.**Disadvantages** : absorption may be delayed, reduced or even enhanced after food or slow or irregular after drugs that inhibit gut motility.. Some drugs are not absorbed and some drugs are destroyed in the gut

Sublingual or buccal administration

Advantages are that quick effect is obtained, e.g. with glyceryl trinitrate.

Disadvantages are the inconvenience if use has to be frequent, irritation of the mucous membrane and excessive salivation which promotes swallowing, so losing the advantages of by passing pre systemic elimination.

Rectal administration

.**Advantages** are that a drug that is irritant to the stomach can be given by suppository (indomethacin); the route is suitable in vomiting, motion sickness, migraine or when a patient cannot swallow, and when cooperation is lacking (sedation in children).

Disadvantages psychological in that the patient may be refuced this route ,rectal inflammation may occur with repeated use and absorption can be unreliable, especially if the rectum is full of faece

Advantages And Disadvantages Of Parenteral Administration

Intravenous (bolus or infusion)

Advantages

Fast ,effective and highly predictable blood concentration and allows rapid modification of dose is suitable for administration of drugs that are not absorbed from the gut and irritant to be given by other routes.

Disadvantages

are the hazard if a drug is given too quickly, as plasma concentration may rise. . Local venous thrombosis is liable to occur with irritant formulations, especially if small veins are used. Infection of the intravenous catheter and the small thrombi on its tip are also a risk during prolonged infusions.

Intramuscular injection

Advantages

This route is reliable, suitable for irritant drugs, and depot preparations(hormonal contraceptives). Absorption is more rapid than subcutaneous injection (soluble preparations are absorbed within 10-30 min).

Disadvantages

are that the route is not acceptable for self-administration, it may be painful, and if any adverse effects occur to a depot formulation, it cannot be removed.

Subcutaneous injection

Advantages is reliable and is acceptable for self-administration.

Disadvantages are poor absorption. Repeated injections at one site can cause lipoatrophy

By inhalation

Advantages are that drugs as gases can be rapidly taken up or eliminated, that has marked the use of this route in general anesthesia from its earliest days. Self-administration is practicable. provide high local concentration minimizing systemic effects.

Disadvantages special apparatus is needed (patients difficult use) drug must be nonirritant if the patient is conscious. Obstructed bronchi

Topical application

For local effect, e.g. to skin, eye, lung, anal canal, rectum, vagina. Advantage high local concentration with low systemic effect . Disadvantage is that absorption can occur, especially when there is tissue destruction so that systemic effects result, e.g. adrenal steroids and neomycin to the skin, atropine to the eye. Ocular administration may cause systemic effects

For systemic effect. Transdermal delivery systems (TDS) release drug through a rate-controlling membrane into the skin and so into the systemic circulation. Fluctuations in plasma concentration associated with other routes of administration are largely avoided, as is first-pass elimination in the liver. Glyceryl trinitrate stmenopausal hormone replacement therapy may be given by this way.

Distribution

If a drug is required to act throughout the body or to reach an organ , it must be go into the blood and into other body compartments. Most drugs distribute widely, part dissolved in body water, part bound to plasma proteins, in part to tissues. drugs bind selectively to plasma or tissue proteins or localised within ogans.**;**

The extent (amount) and strength (tenacity) of protein or tissue binding (stored drug) will affect its duration of action

Metabolism

Metabolism is a general term for chemical transformations occur within the body and its processes change drugs by reducing lipid solubility to enhance elimination and alter a biological activity.

1. Conversion of a pharmacologically *active* to an *inactive*

2. Conversion of one pharmacologically *active* to another *active*

3 Conversion of a pharmacologically *inactive* to *active* sub *prodrugs*

THE METABOLIC PROCESSES

The liver is by far the most important drug metabolising organ, although a number of tissues, including the kidney, gut mucosa, lung and skin also contribute

Phase 1 metabolism a change in the drug molecule by oxidation, reduction or hydrolysis

Phase II water-soluble conjugate which is readily eliminated by the kidney . almost invariably terminates bilogical activity.

Dose:

Sub Therapeutic dose:

Therapeutic dose:

Minimum dose:

Maximum dose:

Toxic dose :

Fatal dose:

Median effective dose (ED50**):** the dose at which 50% of individuals exhibit the specified effect.

Median toxic dose (TD50): the dose required to produce a particular toxic effect in 50% of animals

Median lethal dose (LD50**):**

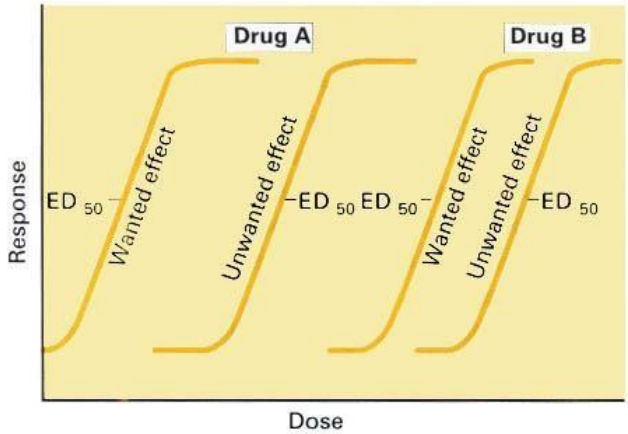
the dose required to produce death in 50% of animal

Duration of action :Time from beginning of drug action to end

Onset of drug action :Time from drug administration to appearance of action

T1/2 Time required to decrease drug amount in blood to half

Bioavailability:Fraction of unchanged drug in blood to dose administered .



When the dose of a drug is increased progressively, the desired response in the patient usually rises to a maximum beyond which further increases in dose elicit no greater benefit but induce only unwanted effects. This is because a drug does not have a single dose-response curve, but a different curve for *each action*, wanted as well as unwanted. unwanted actions are recruited if dose is increased after the maximum therapeutic effect. the concept of the therapeutic index or ratio as the maximum tolerated dose divided by the minimum curative dose

Different responses

Individuals may vary considerably in their responsiveness to Drug; a single individual may respond differently to the same drug at different times during the course of treatment.

The idiosyncratic are usually caused by genetic differences in metabolism of the drug or by immunologic mechanisms, including allergic reactions. An individual patient is **hypo reactive** or **hyperactive** to a drug in that the intensity of effect of a given dose of drug is diminished or increased in comparison to the effect seen in most individuals.

Elimination Removed of drug from body by Renal , hepatic , pulmonary elimination

Introduction to Autonomic Pharmacology

The nervous system is divided into central nervous system (CNS; the brain and spinal cord)and the peripheral nervous system(nervous tissues out side the CNS). The motor nervous system can be divided into. The somatic division is largely concerned with consciously controlled functions such as movement, posture.),The autonomic nervous system (ANS) is largely autonomous (independent) in that its activities are not under direct conscious control.It is concerned primarily with visceral functions—cardiac output, blood flow to various organs, digestion, etc—that are necessary for life.

. In the nervous system, chemical transmission occurs between nerve cells and between nerve cells and their effectors cells. Chemical transmission takes place through the release of small amounts of transmitter substances from the nerve terminals into the synaptic cleft.

By using drugs that mimic or block the actions of chemical transmitters, we can selectively modify many autonomic functions. These functions involve a variety of effectors tissues, including cardiac muscle, smooth muscle, vascular endothelium, exocrine glands, and pre synaptic nerve terminals. Autonomic drugs are useful in many clinical conditions. Conversely, a very large number of drugs used for other purposes have unwanted effects on autonomic function.

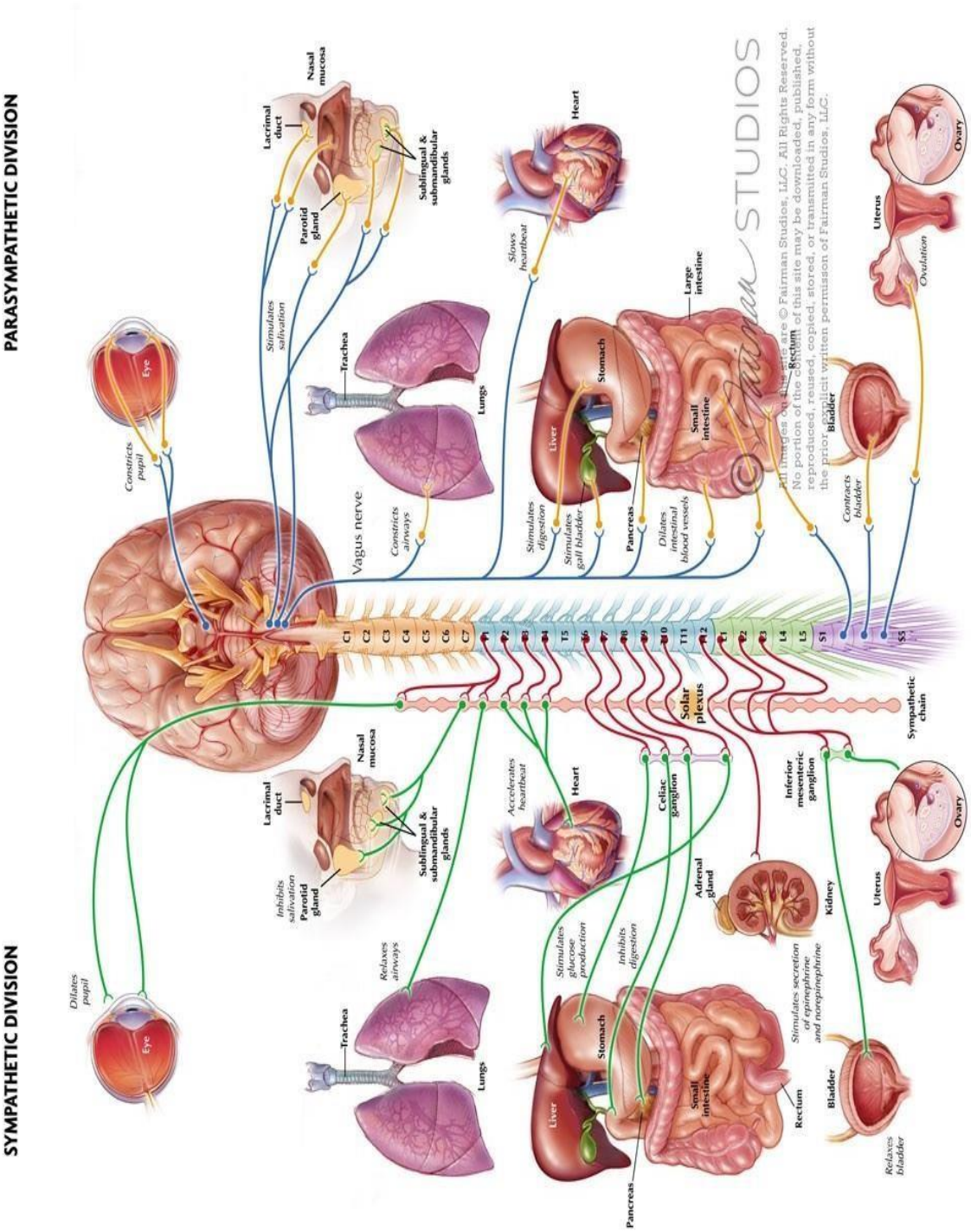
Anatomy of the Autonomic Nervous System

The autonomic nervous system division into two major portions: the **Sympathetic (Thoraco-lumbar)** division and the **Parasympathetic (cranial-sacral)** originate in nuclei within the central nervous system and give rise to preganglionic efferent fibers that exit from the brain stem or spinal cord and terminate in motor ganglia. Sympathetic preganglionic fibers leave the central nervous system through the thoracic and lumbar spinal nerves. The parasympathetic pre ganglion fibers leave the central nervous system through the cranial nerves (third, seventh, ninth, and tenth) and third and fourth sacral spinal

Neurotransmitter Chemistry of the Autonomic Nervous System

An important classification of autonomic nerves is based on the primary transmitter molecules—acetylcholine or norepinephrine—released from terminal fibers .A large number of peripheral autonomic nervous system fibers synthesize and release acetylcholine; they are **cholinergic** fibers, these include all preganglionic efferent autonomic fibers and the somatic (non autonomic) motor fibers to skeletal muscle as well. Thus, almost all efferent fibers leaving the central nervous system are cholinergic. In addition, most parasympathetic postganglionic and a few sympathetic postganglionic fibers are cholinergic.. Most postganglionic sympathetic fibers release norepinephrine (noradrenalin); they are **noradrenergic** (often called simply "adrenergic") fibers—i.e., they act by releasing norepinephrine., a few sympathetic fibers release acetylcholine.. Adrenal modularly cells, which are embryologically analogous to postganglionic sympathetic neurons, release a mixture of epinephrine and norepinephrine.

Five key features of neurotransmitter function represent potential targets of pharmacologic therapy: synthesis, storage, release, activation of receptors, and termination of action


PARASYMPATHETIC DIVISION
SYMPATHETIC DIVISION
Eye
Constricts pupil
Dilates pupil
Nasal mucosa
Lacrimal duct
Parotid gland
Sublingual & submandibular glands
Stimulates salivation
Inhibits salivation
Trachea
Lungs
Vagus nerve
Constricts airways
Relaxes airways
Heart
Slows heartbeat
Accelerates heartbeat
Liver
Stomach
Pancreas
Small intestine
Large intestine
Rectum
Stimulates digestion
Stimulates gall bladder
Dilates intestinal blood vessels
Stimulates glucose production
Inhibits digestion
Bladder
Contracts bladder
Relaxes bladder
Uterus
Ovary
Ovulation
Kidney
Adrenal gland
Stimulates secretion of epinephrine and norepinephrine
Celiac ganglion
Solar plexus
Inferior mesenteric ganglion
Sympathetic chain
C1
C2
C3
C4
C5
C6
C7
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
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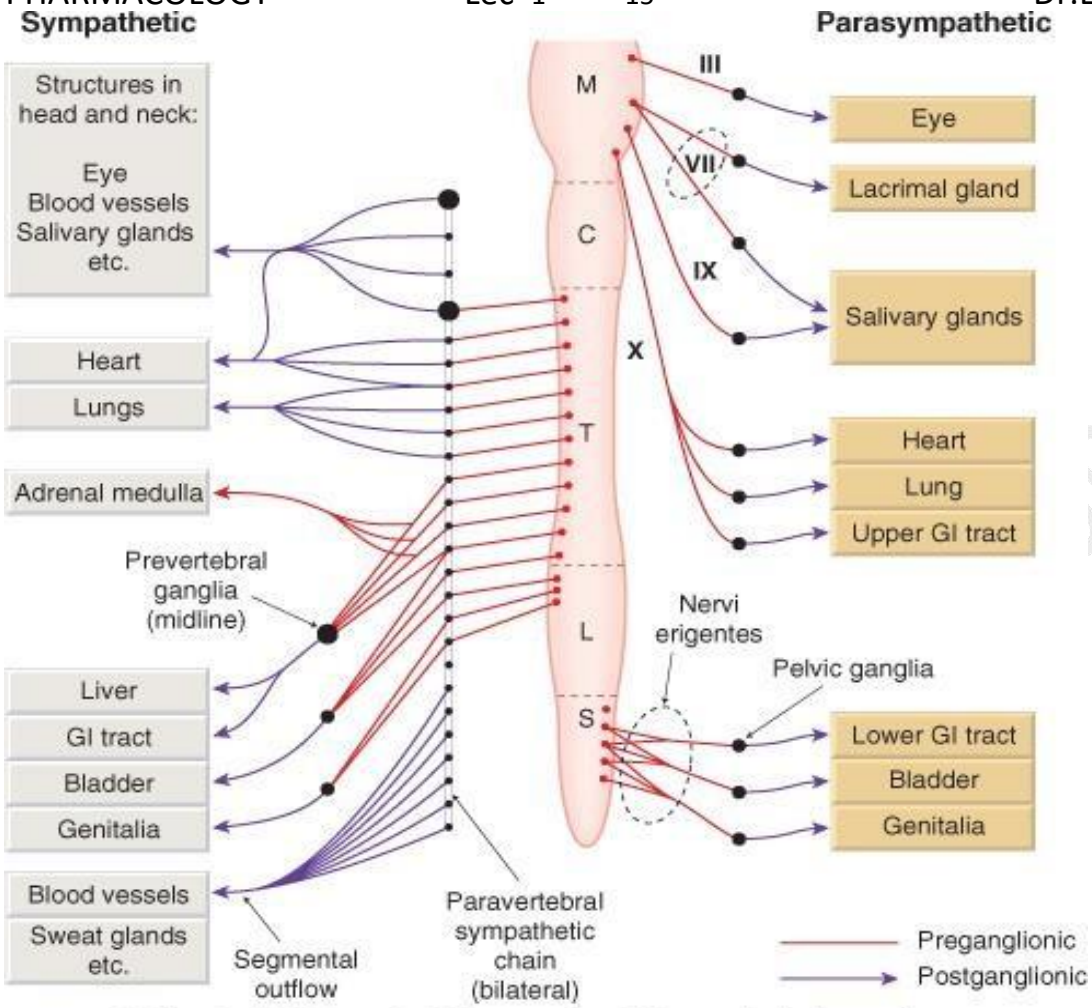

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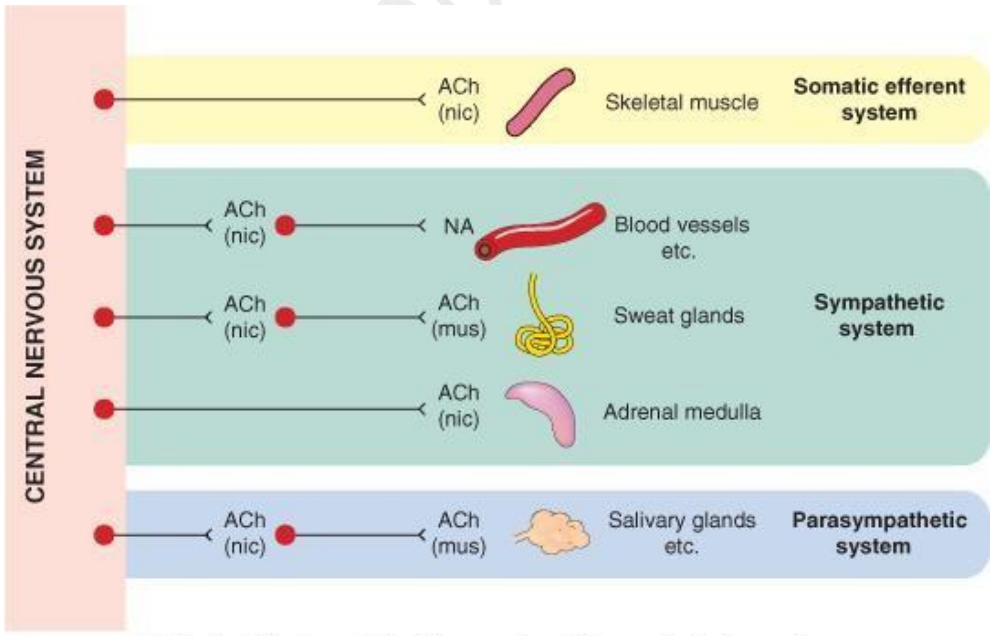

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Cholinergic and – Anticholinergic Drugs

Acetylcholine is a widespread chemotransmitter in the body, mediating a broad range of physiological effects. There are two distinct classes of receptor for acetylcholine defined on the basis of their activation by the alkaloids, nicotine (from tobacco) and muscarine (from a fungus, Amanita muscaria).

At cholinergic nerve endings and in erythrocytes there is an enzyme that destroys acetylcholine, *true cholinesterase* or *acetyl cholinesterase*. In various tissues, especially plasma, there are other esterase which are not specific for acetylcholine but which also destroy other esters These are called nonspecific or *pseudo cholinesterase*

Stimulation of cholinoceptors in autonomic ganglia and at the postganglionic endings affects chiefly the following organs:

Eye: meiosis and spasm of the ciliary muscle occur so that the eye is accommodated for near vision. Intraocular pressure falls.

Exocrine glands: there is increased secretion of the salivary, lachrymal, bronchial and sweat glands. The last are cholinergic, although anatomically part of the sympathetic system; some sweat glands, e.g. auxiliary, may be adrenergic.

Heart: bradycardia with atrioventricular block and eventually cardiac arrest.

Bronchi: there is bronchoconstriction and mucosal hyper- secretion that may be clinically serious in asthmatic subjects, in whom cholinergic drugs should be avoided, as far as possible.

Gut:

motor activity is increased and may cause colicky pain. Exocrine secretion is increased. Tone in anal sphincters falls which may cause defecation

Bladder and ureters contract and the drugs promote micturition.

Neuromuscular (voluntary) junction: neuromuscular junction a cholinergic nerve ending and so is activated causing muscle fasciculation.

Cholinergic drugs(cholinomimetics)

These drugs act on postsynaptic acetylcholine receptors at all the sites in the body where acetylcholine is the effective neurotransmitter.

CLASSIFICATION

Direct-acting (receptor agonists)

Choline esters act at all sites like ACH

Alkaloids which act selectively on end-organs of postganglionic, cholinergic neurons.

Indirect-acting

Cholinesterase inhibitors, or anticholinesterases (physostigmine, neostigmine, pyridostigmine, donepezil), which inhibit the enzyme that destroys acetylcholine, allowing the endogenous transmitter (acetylcholine) to persist and produce intensified effects.

CHOLINE ESTERS

Acetylcholine

Since acetylcholine has such great importance in the body it is not use it in therapeutics by due to rapid distraction by cholinesterase

Carbachol

is not destroyed by cholinesterase actions most pronounced on the bladder and gastrointestinal tract, used now much diminished.,

Bethanechol

resembles carbachol in its actions but is some 10-fold less potent and has no significant nicotinic effects at clinical doses

Alkaloids

Nicotine

is a social drug use as an adjunct to stopping its own abuse as tobacco. It is available as gum to chew, as dermal patches , inhalation.

Pilocarpine

acts directly on end-organs innervated by postganglionic nerves (parasympathetic system plus sweat glands). The chief clinical use of pilocarpine is to lower intraocular pressure in chronic simple glaucoma,; it produces miosis, opens drainage channels improves the outflow of aqueous humour. Oral pilocarpine is available for the treatment of xerostomia (dry mouth) in Sjogren's syndrome, or following irradiation of head and neck tumours. The commonest adverse effect is sweating**.**

ANTICHOLINESTERASES

Chemicals which inactivate esterases (anticholinesterases) are used in medicine and in agriculture as pesticides. They act by allowing naturally synthesized acetylcholine to accumulate instead of being destroyed.

Physostigmine

is an alkaloid, acts for a few hours. Physostigmine is used synergistically with pilocarpine to reduce intraocular pressure. It has been shown to have some efficacy in improving cognitive function in Alzheimer-type dementia

Neostigmine

(tl/2 2 h) is a synthetic reversible anticholinesterase . principally used in myasthenia gravis, to stimulate the bowels and bladder after surgery, and as an antidote to competitive neuromuscular blocking agents. Neostigmine is effective orally, and by injection (usually s.c.).

Pyridostigmine (mestinone)

is similar to neostigmine but has a less powerful action that is slower in onset and slightly longer in duration, It is used in myasthenia gravis

.Donepezil and rivastigmine

A more recent anticholinesterase drugs has been to improve cognitive function in patients with Alzheimer's disease

Anticholinesterase poisoning

The anticholinesterases used in therapeutics are Reversibly inactivate cholinesterase only for a few hours. Poisoning with reversible anticholinesterases is appropriately treated by atropine and the necessary general support; it lasts only hours. In poisoning with irreversible agents the organophosphate insecticide irreversibly inactivate cholinesterase which used in agricultural, industrial, also used in war called nerve 'gas'

Features of acute poisoning

involve the gastrointestinal tract (salivation, vomiting, abdominal cramps, diarrhea, involuntary defecation), the respiratory system (bronchorrhoea, bronchoconstriction, cough, wheezing, dyspnoea), the cardiovascular system (bradycardia), the genitourinary system (involuntary micturition). Death is due to a respiratory failure (SLUDAGE M M)

Treatment.

Contaminated clothing should be removed and the skin washed. Gastric lavage is needed if any of the substance has been ingested. Atropine; 2 mg is given i.m. or i.v. as soon as possible and repeated every 15-60 min. Enzyme reactivation pralidoxime, 1 g of which should be given 4-hourly i.m. or (diluted) by slow i.v. infusion.

Anticholinergic Drugs

Acetylcholine antagonists (blockers) that block the nicotine-like effects (neuromuscular blockers and autonomic ganglion blockers). Acetylcholine antagonists that block the muscarine-like effects, e.g. atropine, are called anticholinergics. The more precise term antimuscarinic is preferred here

Antinicotinic drug

Ganglion-blocking drugs

These agents competitively block the action of acetylcholine and similar agonists at nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia.. The ganglion-blocking drugs are important and used in pharmacologic and physiologic research because they can block all autonomic outflow. However, their lack of selectivity confers such a broad range of undesirable effects that they have limited clinical use.

Hexamethonium

was developed and was introduced clinically as the first drug effective for management of hypertension,.

Trimethaphan, a short-acting ganglion blocker, is inactive orally and is given by intravenous infusion.

Neuromuscular blocking. Drugs

There are two principal mechanisms by which drugs used clinically interfere with neuromuscular transmission:

By competition with acetylcholine
(atracurium, pancuronium, rocuronium, vecuronium).
These drugs are competitive antagonists of acetylcholine

By depolarization of the motor endplate
Such agonist drugs activate the acetylcholine receptor on the motor endplate
(suxamethonium).

USES OF NEUROMUSCULAR BLOCKING DRUGS

1-They are used to provide muscular relaxation during surgery and occasionally to assist mechanical ventilation in intensive therapy units.

2- They are used during electroconvulsive therapy to prevent injury to the patient due to excessive muscular contraction.

Antimuscarinic drugs

which act principally at postganglionic cholinergic (parasympathetic) nerve endings ,

Muscarinic receptors can be subdivided according to their principal sites,

namely in the brain and gastric parietal cells (M1),

heart (M2)

and glandular and smooth muscle cells (M3).

Atropine

Atropine is an alkaloid from the plant (Atropa belladonna).

Atropine is the prototype drug of this group

In general, the effects of atropine are inhibitory but in large doses it stimulates the CNS.

Atropine also blocks the muscarinic effects of cholinergic drugs both peripherally and on the central nervous system.

The clinically important actions of atropine at parasympathetic postganglionic nerve endings are mostly the opposite of the activating effects on the parasympathetic system produced by acetylcholine and cholinergic drug

It does not oppose cholinergic effects at the neuromuscular junction or significantly at the autonomic ganglia,.

Exocrine glands.

All secretions except milk are diminished. Dry mouth , dry eye. Gastric acid secretion is reduced, Bronchial secretions are reduced

Smooth muscle

is relaxed. the gastrointestinal tract there is reduction of tone and peristalsis. Atropine relaxes bronchial muscle, that is useful in some asthmatics. Micturition is slowed and urinary retention may be induced

Ocular effects.

Mydriasis occurs with a rise in intraocular pressure in eyes. An attack of glaucoma may be induced. The ciliary muscle is paralysed and so the eye is accommodated for distant vision.

Cardiovascular system.

Atropine reduces vagal tone thus increasing the heart rate, and enhancing conduction in the bundle of His .Atropine has no significant effect on peripheral blood vessels in therapeutic doses

Other antimuscarinic drugs

Hyoscine (scopolamine)

is structurally related to atropine. Elderly patients are often confused by hyoscine and so it is avoided in their anesthetic premedication. Mydriasis is also briefer than with atropine.

Hyoscine butylbromide(Buscopan)

an effective relaxant of smooth muscle, , the pyloric antral region and the colon, which properties are utilized by radiologists and endoscopic. It useful for colic

Homatropine

is used for its ocular effects (1% and 2% solutions as eye drops). Its action is shorter than atropine

Ipratropium (Atrovent)

used by inhalation as a bronchodilator, can be useful when cough is a pronounced symptom in asthmatic patient.

Flavoxate is used for urinary frequency, because it increases bladder capacity and reduces unstable detrusor contractions

Oxybutynin is also used for detrusor instability, but antimuscarinic adverse effects may limit its value.

Pharmacokinetics.

Atropine is readily absorbed from the gastrointestinal tract and may also be injected by the usual routes.. Atropine is in part destroyed in the liver and in part excreted unchanged by the kidney. for chronic use it has largely been replaced by other antimuscarinic drugs..Poisoning with atropine (and other antimuscarinic drugs) presents with obvious dry mouth (with dysphagia), mydriasis, blurred vision, hot, flushed, dry skin, and, , hyperthermia, restlessness, anxiety, excitement, hallucinations, delirium, mania. and coma

Therapeutic Applications

1-CENTRAL NERVOUS SYSTEM DISORDERS

a- Parkinson's disease:

useful as adjunctive therapy in some patients.

b- Motion sickness:

Certain vestibular disorders respond to antimuscarinic drugs (Scopolamine is effective and more recently introduced agent. given by injection, by mouth, or as a TDS

2- OPHTHALMOLOGIC DISORDERS.

antimuscarinic agents, administered topically, are very helpful in doing a complete examination .Antimuscarinic drugs should never be used for mydriasis unless cycloplegia or prolonged action is required

3. RESPIRATORY DISORDERS

The use of atropine became part of routine preoperative medication because these irritant anesthetics markedly increased airway secretions**.** **(Ipratropium)**, a synthetic analog of atropine, is used as an inhalational drug in asthma.

4- CARDIOVASCULAR DISORDERS

Marked reflex vagal stimulation may depress sinoatrial or atrioventricular node function sufficiently to impair cardiac output. Parenteral atropine or a similar antimuscarinic drug is appropriate therapy in this situation

5- GASTROINTESTINAL DISORDERS:

Antimuscarinic agents can provide relief in abdominal colic ,a traveler's diarrhea and other mild or self-limited conditions of hypermotility. They are often combined with an opioid antidiarrheal drug. Antimuscarinic agents are now rarely used for peptic ulcer disease

6- URINARY DISORDERS

Atropine and other antimuscarinic drugs have been used to provide symptomatic relief in the treatment of urinary urgency caused by minor inflammatory bladder disorders **Oxybutynin**, selective for M3 receptors, is used to relieve bladder spasm after urologic surgery,. improve bladder capacity and continence

7-. OTHER APPLICATIONS

Hyperhidrosis (excessive sweating) reduced by antimuscarinic agents.

SIDE EFFECT

At higher concentrations, atropine causes block of all parasympathetic functions. However, atropine is a remarkably safe drug in adults produce dry mouth, mydriasis, tachycardia, hot and flushed skin, agitation, and delirium for as long as a week. Body temperature is frequently elevated.

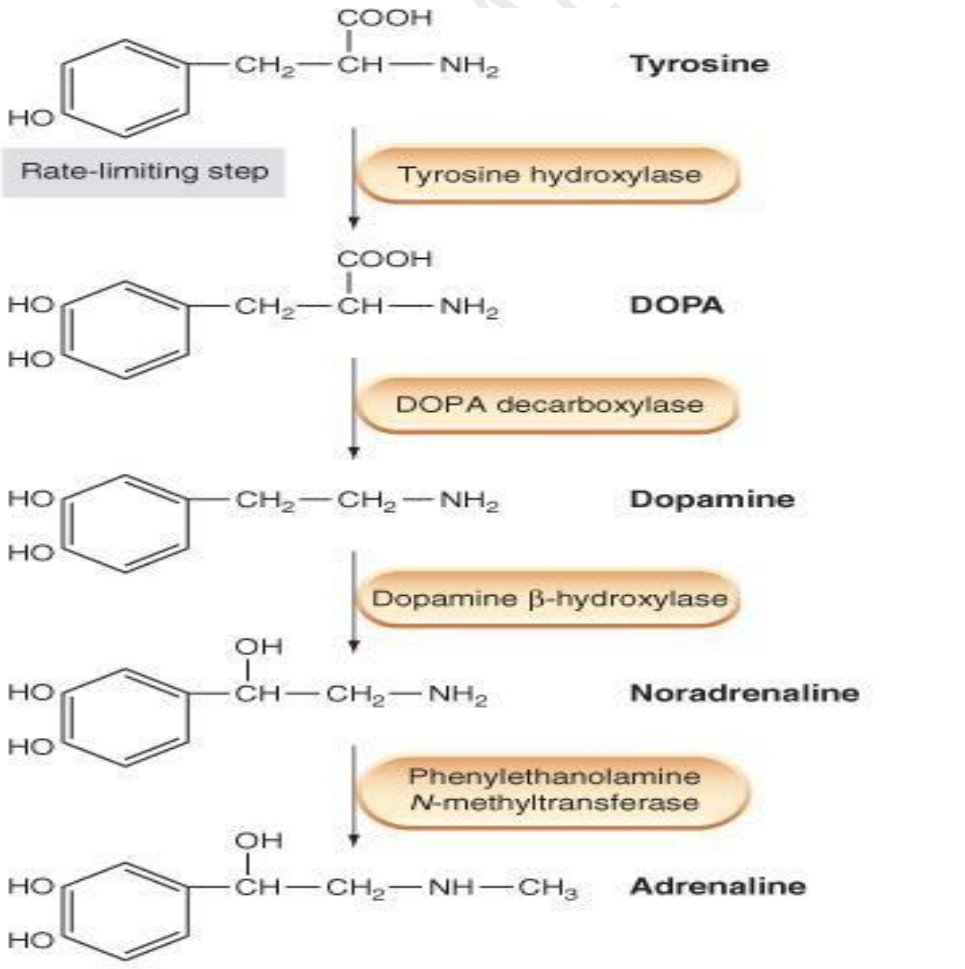
Contraindications.

Antimuscarinic drugs are contraindicated in patients with **glaucoma,.In elderly men**, antimuscarinic drugs should always be used with caution and should be avoided in those with a history of **prostatic hyperplasia**, **BPH** ,**Pyloric stinosis** ,**Bladder neck obstraction**

Adrenergic mechanisms

The sympathetic nervous system is an important regulator of the activities of organs .The effects of sympathetic stimulation are mediated by release of catecholamine(Adrenaline, noradrenalin and dopamine) from nerve terminals that to activate the adrenoceptors on postsynaptic sites. Also in response to a variety of stimuli such as stress, the adrenal medulla releases Adrenaline, noradrenalin transported in the blood to target tissues.

Catecholamine are formed in the body. The natural synthetic path is:
Tyrosine —> Dopa —> Dopamine —> Noradrenalin —>Adrenaline



The termination of action of catecholamine released at nerve endings by

1-Reuptake into nerve endings where it is stored also subject to MAO mono amino oxidase degradation

2- Diffusion away from the area of the nerve ending and the receptor

3- Metabolism (by extra neuronal MAO and catechol-o-methyltransfrase COMT)

ADRENOCEPTORS

BETA (β) ADRENOCEPTORS

Subtypes of β receptors, designated(β_1),(β_2) and(β_3) receptors

ALPHA ADRENOCEPTORS

two major groups of a receptors a_1 and a_2 (Auto receptor)

DOPAMINE RECEPTORS

The dopamine receptor subtypes, termed D_1 ,D_2, D_3, D_4, and D_5

SELECTIVITY FOR ADRENOCEPTORS

The classification of sympathomimetics and antagonists is based on selectivity for receptors and on use.

But selectivity is relative, not absolute;

some agonists act on both a- and β receptors.

ADRENERGIC DRUGS

Directly By binding on adrenoceptors: as agonists(**adrenaline**) or antagonists (**propranolol***)*

Indirectly Sympathomimetic drugs

1-Discharging noradrenalin stored in nerve endings (**amphetamine)**

2-By preventing reuptake into the adrenergic nerve ending of released noradrenaline and dopamine (**cocaine, tricyclic antidepressants andnoradrenaline-selective reuptake inhibitors**

3- By preventing the destruction of catecholamine in the nerve ending (**mono amine oxidase**) inhibitors

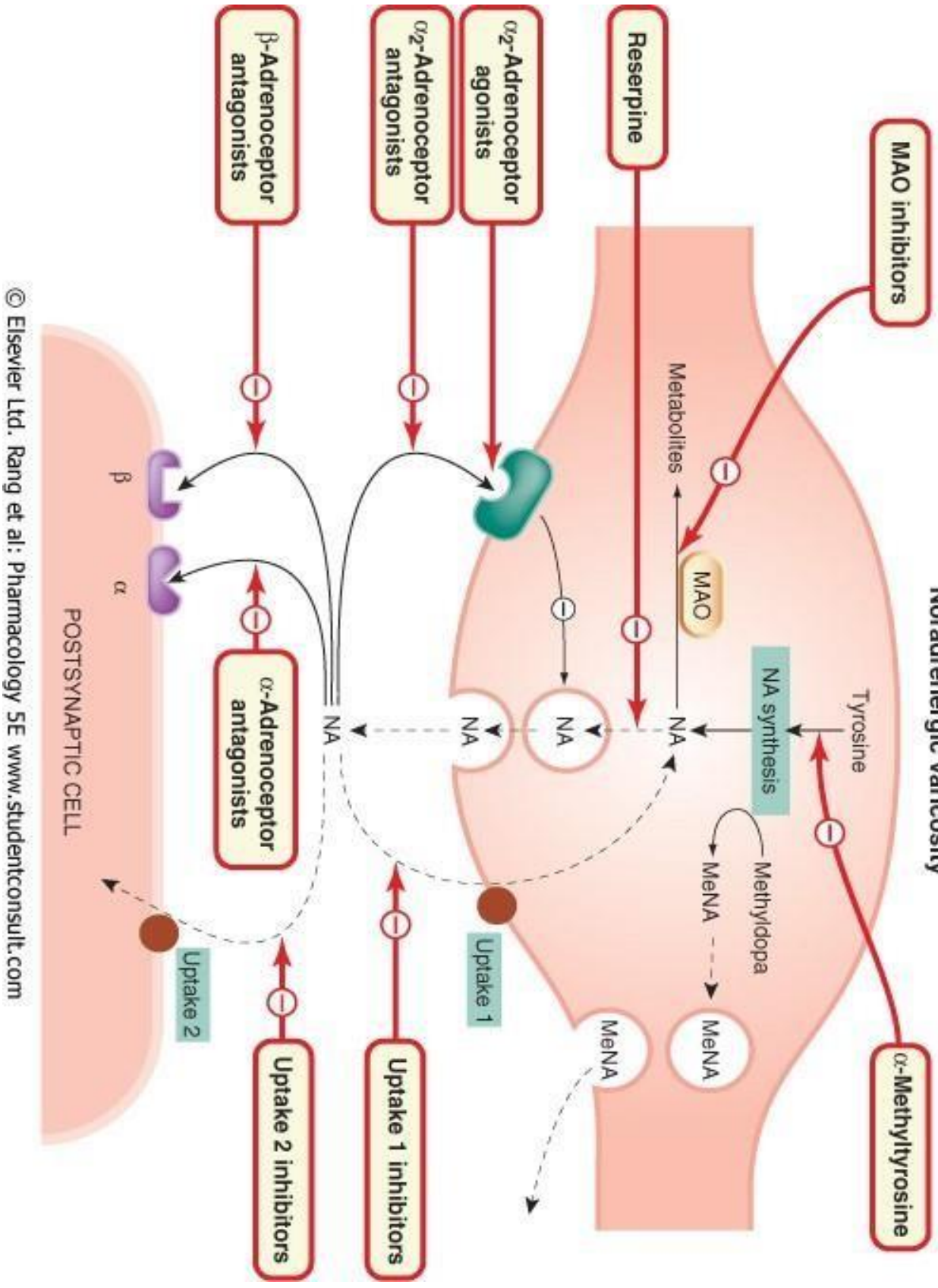
4-By depleting the stores of noradrenalin in nerve endings (**reserpine**)

5-By preventing the release of noradrenalin from nerve endings in response to a nerve impulse (**guanethidine)**

6-By activation of adrenoceptors on adrenergic nerve endings that inhibit release of noradrenaline (α2 autoreceptors) (**clonidine**)

7-By blocking sympathetic autonomic ganglia(**trimetaphan**).

8- False neurotransmeters (**Methyl dopa**)


Noradrenergic varicosity
MAO inhibitors
Reserpine
α2-Adrenoceptor agonists
α2-Adrenoceptor antagonists
β-Adrenoceptor antagonists
α-Methyltyrosine
Tyrosine
NA synthesis
Methyldopa
MeNA
MAO
Metabolites
NA
MeNA
MeNA
NA
NA
NA
Uptake 1
Uptake 1 inhibitors
α-Adrenoceptor antagonists
Uptake 2 inhibitors
Uptake 2
β
α
POSTSYNAPTIC CELL
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SYMPATHOMIMETIC DRUGS

Drugs that mimic the actions of catecholamine have a wide range of effects, can be grouped by mode of action , receptors that they activate.

Cardiovascular System

A. BLOOD VESSELS: Alpha receptors increase arterial resistance, whereas β_2 receptors promote smooth muscle relaxation

B. HEART: Stimulation of β receptors increases rate , cardiac output

C. BLOOD PRESSURE: The effects on blood pressure can be explained on the basis of their effects on the heart, blood vessels

Eye: The radial papillary dilator muscle of the iris contains α ,β receptors; activation causes mydriasis

Respiratory Tract : Bronchial smooth muscle contains β_2 receptors that cause relaxation. Activation of these receptors results in bronchodilation

Gastrointestinal Tract: Relaxation of GIT smooth muscle by α ,β stimulant agents

Genitourinary Tract:

uterus contains β2 receptors. mediate relaxation clinically useful in pregnancy .The bladder base, urethral sphincter, and prostate contain α receptors that mediate contraction and promote urinary continence. β 2 receptors of the bladder wall mediate relaxation.

Metabolic Effects:

Activation of β3 in fat cells increased lipolysis.

Effects on Endocrine Function:insulin secretion is stimulated by β receptors and inhibited by α_2 receptors.

Individual sympathomimetics Catecholamine

Adrenaline (epinephrine) (α - and β-adrenoceptor effects)

very potent vasoconstrictor and cardiac stimulants used:

1- as a vasoconstrictor i.e. with local anesthetics

2 as a topical mydriatic

3-for severe allergic reactions, i.m., i.v. (or s.c.)

4- Adrenaline is used in anaphylactic shock

Noradrenaline (norepinephrine)

(chiefly α and ,β effects) .The main effect of administered noradrenaline is to raise the blood pressure by constricting the arterioles and so raising the total peripheral resistance

Dopamine and Dobutamine It is useful in shock and in low output heart failure

NONCATECHOLAMINES

Ephedrine

Ephedrine is indirect sympathomimetic actions Ephedrine can be used as a bronchodilator, in heart block, as a mydriatic and as a mucosal vasoconstrictor, but newer drugs, which are often better for these purposes, are displacing it

Pseudoephedrine is similar to Ephedrine

Phenylephrine

has longer duration of action, up to an hour. It can be used as a nasal decongestant but sometimes irritates.

Salbutamol (Ventolin)

is taken orally, 2-4 mg up to 4 times/day; it also acts quickly by inhalation and the effect can last as long as 4h, which makes it suitable for both prevention and treatment of asthma. premature labour. (Salmeterol have low onset and long duration of action)

Mucosal decongestants

Nasal and bronchial decongestants (vasoconstrictors) are used in allergic rhinitis, colds, coughs and sinusitis, , as nasal drops sprays. All the sympathomimetic vasoconstrictors, have used for the purpose,. Ischaemic damage to the mucosa is possible if they are used excessively (more often than 3-hourly) or for prolonged periods (> 3 weeks) The occurrence of rebound congestion is also liable to lead to overuse ephedrine 0.5% , phenylephrine 0.5%, Xylometazoline 0.1% (Otrivine) should be used, if at all, for only a few days since longer application reduces the ciliary activity and will lead to rebound congestion.

hock

A state of inadequate capillary perfusion (oxygen deficiency) of vital tissues to an extent that adversely affects Vital function, heart(pump blood) brain (consciousness, respiration) , kidney (urine formation):

- Treatment of the cause: bleeding, infection,
- Replacement of any fluid lost from the circulation
- Perfusion of vital organs (brain, heart, kidneys)
- Maintenance of the mean blood pressure and Blood flow

Adrenoceptor Antagonist Drugs

Alpha-receptor antagonists drugs

Alpha-receptor antagonists may be reversible or irreversible in their interaction with these receptors. are examples of reversible antagonists Phentolamine ,prazosin Terazosin Doxazosin, Tamsulosin alfuzosin **Phenoxybenzamine**, an irreversible blockade

Pharmacologic Effects

A. CARDIOVASCULAR EFFECTS

α -receptor antagonist drugs cause a lowering of peripheral vascular resistance and lowering blood pressure.

B. OTHER EFFECTS

Minor effects that the blockade of α receptors in other tissues include miosis and nasal stuffiness.

CLINICAL USES

Pheochromocytoma.

Hypertensive Emergencies'

Chronic Hypertension

Peripheral Vascular Disease

Local Vasoconstrictor Excess

Urinary Obstruction

Erectile Dysfunction

BPH

BETA-RECEPTOR ANTAGONIST DRUGS

Beta-receptor antagonists antagonizing the effects of catecholamine's at β adrenoceptors. occupy β receptors and competitively reduce receptor occupancy by catecholamine's and other β agonists.

The major difference among the many β-receptor-blocking drugs concerns their relative affinities for β_1 and β_2 receptors Some of these antagonists have a higher affinity for β_1 than for β_2 receptors, and this selectivity may have important clinical implications. Since none of the clinically available β -receptor antagonists are absolutely specific for β_1 receptors, the selectivity is dose-related; diminish at higher drug conc.

Pharmacologic Effects

A. Effects On The Cardiovascular System

Beta-blocking drugs lower blood pressure in patients with hypertension

B. Effects On The Respiratory Tract

Blockade of the β_2 receptors in bronchial smooth muscle may lead to an increase in airway resistance, particularly in patients with asthma. $Beta_1$-receptor antagonists such as metoprolol and atenolol may have some advantage over nonselective β antagonists. However, no currently available β_1-selective antagonist is sufficiently specific to completely avoid interactions with β_2 adrenoceptors.

C. Effects On The Eye

Several β blocking agents reduce IOP especially in glaucoma

D. Metabolic And Endocrine Effects

Beta-receptor antagonists such as propranolol inhibit lipolysis

E. Effects Not Related To Beta-Blockade

Local anesthetic action, also known as "membrane-stabilizing" action, is a prominent effect of several β blockers.

CLINICAL USES OF THE β RECEPTOR-BLOCKING DRUGS

Hypertension

The Beta -adrenoceptor-blocking drugs have proved to be effective and well tolerated in hypertension. many patients respond to a Beta blocker used alone, the drug is often used with either a diuretic or a vasodilator

Ischemic Heart Disease

Beta-adrenoceptor blockers reduce the frequency of anginal episodes.

Cardiac Arrhythmias

Beta antagonists are often effective in the treatment of both supraventricular and ventricular arrhythmias

Glaucoma

Systemic administration of β -blocking drugs for other indications was reduce intraocular pressure in patients with glaucoma.

Hyperthyroidism

Excessive catecholamine action is an important aspect of the pathophysiology of hyperthyroidism, especially in relation to the heart The β antagonists have beneficial effects relate to blockade of adrenoceptors and perhaps in part to the inhibition of peripheral conversion of thyroxin to triiodothyronine. The latter action may vary from one β antagonist to another. Propranolol has been used extensively in patients with hyperthyroidism

Neurologic Diseases

Several studies show a beneficial effect of propranolol in reducing the frequency and intensity of migraine headache.

.Propranolol may contribute to the symptomatic treatment of alcohol withdrawal in some patients.

Adverse Effects Of B RECEPTOR-BLOCKING DRUGS

The major adverse effects of β-receptor antagonist drugs relate to the consequences of β blockade. $Beta_2$-receptor blockade associated with the use of nonselective agents commonly causes worsening of asthma and other forms of airway obstruction without having these consequences in normal individuals. if at all, in patients with reactive airways. $Beta_1$-selective antagonists are generally well tolerated.

SPECIFIC AGENTS

Propranolol

is the prototype of β -blocking drugs. a nonselective agent with negligible effects at α and muscarinic receptors

Metoprolol, Atenolol

are β_1-selective group. may be safer in patients who experience bronchoconstriction in response to propranolol. Since their β_1 selectivity is rather modest, they should be used with great caution in patients with a history of asthma.).

Timolol

is a nonselective agent with excellent ocular hypotensive effects when administered topically in the eye.

Betaxolol (β_1-selective) for topical ophthalmic application (glaucoma)

Carvedilol : nonselective β -receptor antagonists with some capacity to block α_1-adrenergic receptors

Esmolol is an ultra-short-acting β_1-selective adrenoceptor antagonist

Butoxamine is a research drug selective for β_2 receptors. Selective β_2-blocking drugs have not been actively used because there is no clinicalapplication for them; none is available for clinical use.

PHARMACOLOGY OF C N S DRUGS

The membranes of nerve cells contain two types of channels:.

Voltage-gated channels respond to changes membrane potential of cell.

Ligand-gated channels opened by the binding of neurotransmitters

SITES OF DRUG ACTION

Drugs that act in the CNS produce their effects by modifying some step in chemical synaptic transmission

(1) Action potential in presynaptic fiber

(2) synthesis of transmitter

(3) storage of transmitter

(4) metabolism of transmitter

(5) release of transmitter

(6) reuptake of transmitter

(7) degradation of transmitter

(8) receptor for the transmitter

CENTRAL NEUROTRANSMITTERS

Amino Acids Amino acids **Glutamate** Excitatory Neurotransmitter

Glycine and **GABA**. inhibitory neurotransmitters

Monoamines : catecholamine and 5-hydroxytryptamine(Serotonin)

Peptides include opioid peptides (e.g., enkephalins, endorphins), substance P, **Acetylcholine**

CNS DEPRESSANT

BASIC PHARMACOLOGY OF SEDATIVE-HYPNOTICS

Anxiety states and sleep disorders are common problems,

An effective **sedative** (anxiolytic) agent should reduce anxiety and exert a calming effect. A **hypnotic** drug should produce drowsiness and sleep. Hypnotic effects involve more depression of the central nervous system than sedation, and this can be achieved with many drugs.

The benzodiazepines are widely used sedative-hypnotics.

Alprazolam Chlordiazepoxide Clonazepam Diazepam Lorazepam other Barbiturate, Meprobamatees.

MOA of Benzodiazepines, Barbiturates, Newer Hypnotics

The Benzodiazepines, the barbiturates, , and other drugs bind to molecular components of the GABA receptor in neuronal membranes in the CNS.

Benzodiazepines potentiate GABAergic inhibition at all levels of the neuron axis,

The components of the $GABA_A$ receptor-chloride ion channel as

(1)Agonists facilitate GABA actions, and this occurs at multiple BZ binding sites in the case of the benzodiazepines

(2) Antagonists by **flumazenil**, which blocks the actions of BZ,

(3) Inverse agonists by-carbolines

ORGAN LEVEL EFFECTS

1. Sedation BZ, barbiturates, and most sedative-hypnotic drugs exert calming effects with reduction of anxiety at relatively low doses

2. Hypnosis induce sleep in high doses depend on several factors, the specific drug, the dose, and frequency of its administration.

3. Anesthesia high doses of certain sedative-hypnotics depress the central nervous system to the point known as stage III of general anesthesia

4. Anticonvulsant effects Many sedative-hypnotics capable of inhibiting the development and spread of epileptic electrical activity in the CNS

5. Muscle relaxation Some sedative-hypnotics, particularly meprobamate and benzodiazepine groups, exert inhibitory effects on transmission at the skeletal neuromuscular junction. that lead to muscle relaxation

6- Effects on respiration and cardiovascular function at therapeutic doses, sedative-hypnotics can produce significant respiratory depression ,a usual cause of death due to overdose of sedative-hypnotics

Tolerance decreased responsiveness to drug following repeated exposure is a common feature of sedative-hypnotic use.

Physiologic dependence :an altered physiologic state that requires continuous drug administration characterized by states of increased anxiety, insomnia, and central nervous system excitability that may progress to convulsions.

Most sedative-hypnotics including BZ are capable of causing physiologic dependence when used on a long-term.

CLINICAL PHARMACOLOGY OF SEDATIVE-HYPNOTICS

1- Relief of anxiety Insomnia,

2- Sedation and amnesia before and during surgical procedures

3- Diagnostic aids or for treatment in psychiatry

4- Treatment of epilepsy and seizure states

5- Component of balanced anesthesia (intravenous administration)

6- Control of ethanol or other sedative-hypnotic withdrawal states

7- Muscle relaxation in specific neuromuscular disorders

Adverse effects of sedative-hypnotics

Drowsiness, impaired judgment, and diminished motor skills, sometimes with a significant impact on driving ability, job performance, and personal relationships.

Benzodiazepines may cause a significant dose-related amnesia; they can significantly impair ability to learn new information, particularly that involving cognitive processes

Barbiturates

have a low therapeutic index, I. relatively small overdose may danger life; they cause dependence and have been popular drugs of abuse.

1- very short-acting

2- short-acting

3- intermediate-acting drugs

4 -The long-acting Phenobarbital

Uses of barbiturates:

limited to intractable insomnia in patients already taking barbiturates (should be avoided in the elderly). used for epilepsy, thiopental for anaesthesia.

Overdose of barbiturates

hypothermia, respiratory depression and coma.

Nonbenzodiazepine hypnotics

Although structurally unrelated to the benzodiazepines, these drugs act on the same receptor complex but at different sites from BZ

Zopiclone Zolpidem Zaleplon

Chloral hydrate

has a fast (30-60 min) onset of action and duration of action 6-8 h. It is a prodrug, being rapidly metabolised by alcohol dehydrogenase into the active hypnotic trichloroethanol (t1/2 8h is dangerous in serious hepatic or renal failure and aggravates peptic ulcer

PHARMACOLOGY OF ANTISEIZURE DRUGS

Epilepsy

A complex chronic disorder characterized by recurrent seizures. Seizures are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons. The causes of seizures include the full range of neurologic diseases, from infection to neoplasm and head injury. In some subgroups, inheritance has a predominant factor

Antiseizure drugs are act by one of three mechanisms:

(1) Enhancement of GABAergic (inhibitory) transmission,
(2) Diminution of excitatory (usually glutamatergic) transmission
(3) Modification of ionic conductance

The classic major drugs for partial and generalized tonic-clonic seizures are **Phenytoin, Carbamazepine**, **Valproate**, **Barbiturates**.

Newer drugs

Lamotrigine, Levetiracetam, **Gabapentin**, **Oxcarbazepine**, **Pregabalin**, **Topiramate**, **Vigabatrin**, and **Zonisamide**

ANTIDEPRESSANTS

Major depression is one of the most common psychiatric disorders. At any given moment, about 3-5% of the population is depressed and an estimated 10% of people may become depressed during their lives. The symptoms of depression are often unrecognized both by patients and by physicians.

A. TRICYCLIC ANTIDEPRESSANTS (TCAS)

Tricyclic antidepressants- have been used clinically for four decades. **Imipramine** and **Amitriptyline** are the prototypical drugs of the class as mixed norepinephrine and serotonin uptake inhibitors, although they also have several other effects.

B. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

Fluoxetine-an effective and more selective antidepressant with minimal autonomic toxicity.

C. MONOAMINE OXIDASE (MAO) INHIBITORS

Phenelzine and **Isocarboxazid** (no longer marketed); or Tranylcypromine which is itself a weak inhibitor of MAO.

CLINICAL PHARMACOLOGY OF ANTIDEPRESSANTS

A. Depression

B. Anxiety disorders ,panic ,generalized anxiety ,social phobia

C. Chronic pain

D. Enuresis.

E- Eating disorders

F- Smoking cessation

G- Delay orgasm and ejaculation (in borh sexes)

H- PMS ,PMDD

ALCOHOLS

Ethanol is a small molecule that is absorbed rapidly from the gastrointestinal tract. After ingestion of alcohol in the fasting state, peak blood alcohol concentrations are reached within 30 minutes. The presence of food in the gut delays absorption by slowing gastric emptying,. women have a higher peak concentration than men, in part because women have a lower total body water content

.

EFFECT OF ALCOHOLS

Alcohol causes sedation and slurred speech, ataxia, impaired judgment, induces coma, respiratory depression, and death., Significant depression of myocardial contractility has been observed in individuals who acutely consume moderate amounts of alcohol

Consequences of Chronic Alcohol Consumption

A. LIVER AND GASTROINTESTINAL TRACT

Chronic alcohol ingestion is the most common cause of Liver disease, chronic pancreatitis. gastritis. injures the small intestine.

B. NERVOUS SYSTEM

The consumption of alcohol results in tolerance and in physical and psychological dependence(need to repeated drug intake). Consumption of large amounts of alcohol leads to neurologic deficits. generalized symmetric peripheral nerve injury, disturbances and ataxia that are due

to degenerative changes in the central nervous system. dementia, ataxia, and a confused state that can progress to coma and death.

C. CARDIOVASCULAR SYSTEM

Cardiomyopathy, heart failure, Arrhythmias, Hypertension, Coronary heart disease

D. FETAL ALCOHOL SYNDROME

Ethanol rapidly crosses the placenta and reaches concentrations in the fetus that are similar to those in maternal blood. Chronic maternal alcohol drink during pregnancy is associated with teratogenic effects, and alcohol appears to be a leading cause of mental retardation and congenital malformation.

E .INCREASED RISK OF CANCER

Chronic alcohol drink increas risk of cancer of the mouth, pharynx, larynx, esophagus, liver

Alcohol-Drug Interactions

Interactions between ethanol and other drugs can have important clinical effects that result from alterations in the pharmacokinetics or pharmacodynamics of the second drug.

Central Nervous System Stimulants

Many drugs stimulate the CNS, only a few are used therapeutically, and their indications for use are limited. disorders treated with CNS stimulants (Narcolepsy ,Attention Deficit-Hyperactivity Disorder)

Narcolepsy:

is a sleep disorder characterized by daytime –sleep attacks‖ in which the victim goes to sleep at any place or any time. excessive daytime drowsiness, , muscle weakness and hallucinations at onset of sleep, and disturbances of nighttime sleep patterns

Attention Deficit-Hyperactivity Disorder ADHD

It occurs before 7 years of age and is characterized by hyperactivity, a short attention extent restlessness, and irresponsibility. Such behaviors make it difficult for the child to get along with others (e.g., family members, peer groups, teachers) and to function in situations requiring more controlled behavior (e.g., classrooms).

TYPES OF STIMULANTS

Amphetamines , Amphetamine-related drug (methylphenidate)

increase the amounts of catecholamine in the brain, producing mood elevation ,euphoria, increasing mental alertness and capacity for work, decreasing fatigue, and prolonging wakefulness

Overdose of stimulant, include severe agitation, cardiac dysrhythmias, confusion hallucinations, hyperactivity, , insomnia, irritability, nervousness, restlessness, tremors, seizures, coma, circulatory collapse, and death..

Xanthenes'

stimulate the cerebral cortex, increasing mental alertness and decreasing drowsiness and fatigue. myocardial stimulation with increased cardiac output and heart rate, diuresis, and increased secretion of pepsin and hydrochloric acid. Large doses can impair mental and physical functions by producing restlessness, nervousness, anxiety, agitation, insomnia, cardiac dysrhythmias, and gastritis.

ANALGESIA –ANESTHESIA

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage ,also can occur without tissue injury or evident disease and can persist after injury has healed.

TYPES OF PAIN

According to severity

(Mild pain ,Moderate pain ,Severe pain, Over whelming acute pain)

According to type

(Acute pain Transient pain Neuropathic pain Chronic pain)

Acute and transient pain is managed primarily by analgesic drugs. Chronic and neuropathic pain often requires analgesic drugs and adjuvant drugs as well as non drug measures.

Analgesic drug:

a drug that relieves pain due to multiple causes, e.g. paracetamol, morphine., Analgesics are chosen according to the cause of pain and its severity..

Adjuvant drugs

are those used alongside analgesics in the management of pain.

• **Analgesics** are classed as

Narcotic

(which act in the central nervous system and cause drowsiness, i.e. opioids)

Non-Narcotic

(which act chiefly peripherally, e.g. diclofenac).

Narcotic or opioid analgesics

Endogenous opioid peptides (endorphins, dynorphins, Enkephalins) have opioid receptors. when there were no opioids in the body These peptides attach to specific opioid receptors, mainly μ(mu), δ(delta) Ƙ(kappa) located at several spinal and multiple supra spinal sites in the CNS and act to open potassium channels and prevent opening of voltage-gated calcium channels which reduces neuronal excitability , inhibits release of pain neurotransmitters, including substance P…

Morphine and other opioid analgesics principally acts mainly on the μ1 opioid receptor (analgesia, euphoria, dependence) and μ2 – receptors (respiratory depression, reduced gut motility). Pure competitive opioid antagonists, e.g. **naloxone, naltrexone**, block all opioid receptors while exerting no activating effect

The principal actions of morphine:

1-CNS:

- Depression: analgesia, depression of respiratory, Cough reflex, sleep
- Excitation, leading to: vomiting, miosis
- Changes of mood: euphoria or dysphoria
-Dependence; affects other systems too

. 2-Peripheral nervous system: Analgesia, some anti-inflammatory effect

3-Smooth muscle stimulation:

- GI muscle spasm (delayed passage of contents with constipation)
- Biliary tract spasm
- Bronchospasm

4-Cardiovascular system :Dilatation of (arterioles) and (veins)

PRINCIPAL USES OF MORPHINE AND ITS ANALOGUES

• Relief of moderate to severe acute pain

• Premedication ,postoperative analgesia for surgery

• Symptomatic control of acute diarrhea, e.g. travelers" diarrhea (codeine)

• Suppression of cough (codeine)

• Production of euphoria as well as pain relief in the dying.

Classification of opioids by analgesic efficacy

Opioid efficacy	
Low efficacy for mild and moderate pain	**High efficacy for severe pain**
codeine	*buprenorphine
dihydrocodeine	dexromoramide
dextropropoxyphene	diamorphine (heroin)
*nalbuphine	dipipanone
*pentazocine	*meptazinol
	methadone
	morphine
	papaveretum
	pethidine (meperidine)
	phenazocine
	tramadol

*Partial agonist

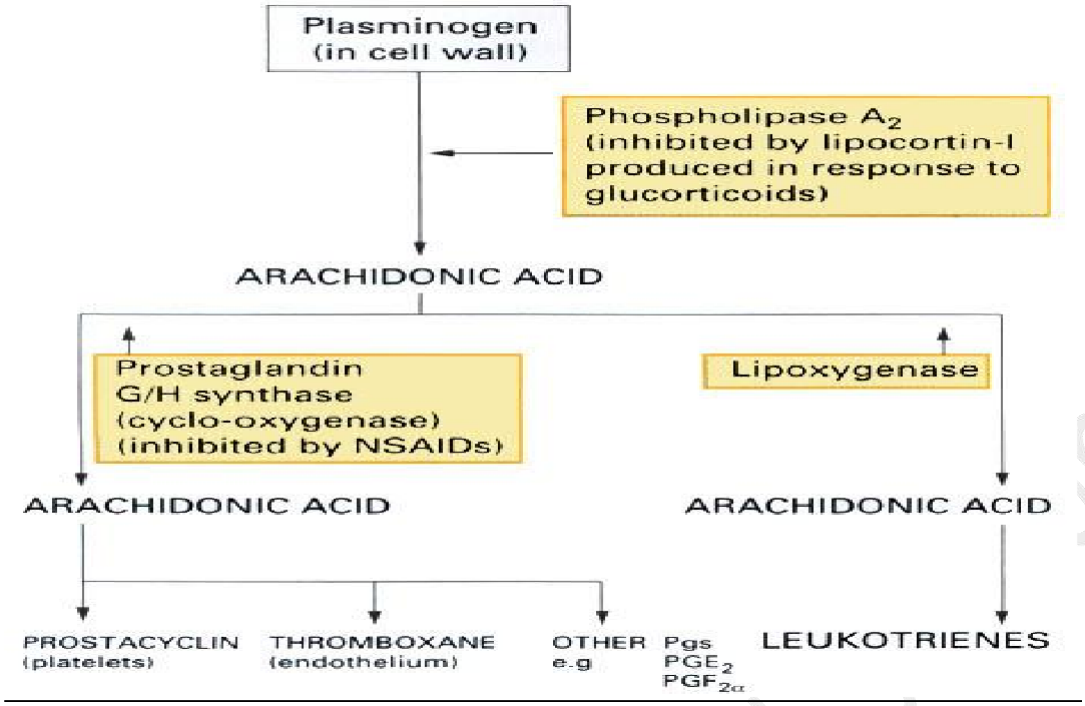
Nonsteroidal anti-inflammatory drugs (NSAIDs)

Inflammation

The clinical features of inflammation as swelling, redness, pain and heat. The underlying mechanisms which produce these symptoms are complex, involving many different cells and cell products. A normal inflammatory response is essential to fight infections and is part of the repair mechanism and removal of debris following tissue damage. Inflammation can also cause disease, due to damage of healthy tissue. at a site of inflammation release compounds which enhance the inflammatory response *cytokines* and ***eicosanoids*** **(**Inflammatory mediators)

Eicosanoids (prostaglandins, thromboxanes, leukotrienes, lipoxins),. derived principally from arachidonic acid in cell walls. • Arachidonic acid is stored mainly in phospholipids of cell walls,

• Arachidonic acid is further metabolized by cyclooxygenase (COX,),



Nonsteroidal anti-inflammatory drugs (NSAIDs) act exert their anti-inflammatory effects by inhibiting COX.(exists as two different types), COX-1 is predominantly present inmost tissues, especially stomach, platelets and kidneys.

COX-2 many cells including macrophages, synoviocytes, chondrocytes, fibroblasts and endothelial cells, and only in low concentration in the gastrointestinal mucosa

NSAIDs differ in their relative inhibition of the two isoforms of COX, recognition of which has lead to the development of selective COX-2 inhibitors. Such drugs have less adverse effects, especially on the gastrointestinal tract

Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

The members of this class of drug, although structurally heterogeneous, possess a mode of action which is to *block prostaglandin synthesis* ,., their key action of inhibiting prostaglandin formation is reflected in the range of effects, beneficial and adverse, which the members exhibit.

NSAIDs may be categorized according to their COX specificity as:

• COX-2 *selective* compounds, for inhibiting COX-2 is at least 5 times that for COX- 1**.(Rofecoxib, Celecoxib Meloxicam, Nabumetone*).***

• *Non- selective* compounds, which comprise all other NSAIDs. These drugs inhibit COX-1 as much as, or even more than, COX-2.

USES

.1- Analgesia: NSAIDs are effective for pain of mild to moderate intensity including musculoskeletal and postoperative pain, and inflammatory arthritis; they have the advantage of not causing dependence, unlike opioids

2- Anti-inflammatory action: this is utilized in all types of arthritis, musculoskeletal conditions.

3- Antipyretic action: PG synthesis in the hypothalamus is blocked, thus reducing fever.

4- Antiplatelet function: aspirin is indicated for the treatment and/or prevention of myocardial infarction, transient ischemic attacks and embolic strokes.

5- Prolongation of gestation and labour:

6-Primary dysmenorrhoea: mefanamic acid used to reduce production of PGs by the uterus which cause uterine hyper contractility and pain.

7-Further areas of potential benefit from NSAIDs are being explored, including the prevention of Alzheimer's dementia and colorectal carcinoma

ADVERSE REACTIONS

Gastrointestinal effects Gastric and intestinal mucosal damage is the commonest adverse effect of NSAIDs. Indigestion, gastro-oesophageal reflux, erosions, peptic ulcer,

Clinical trial evidence in general appears to support the theory that COX-2 selective inhibitors are as effective as, but have fewer adverse effects than, non-COX-2 selective compounds; for example meloxicam is better tolerated than diclofenac or piroxicam

Renal effects

Renal blood flow is reduced ,there salt sodium and fluid retention and arterial blood pressure may rise.

Other general effects

include cholestasis, hepatocellular toxicity, haemolytic anemia.

Urticaria, severe rhinitis and asthma occur in susceptible individuals, e.g. with exposed to NSAIDs, notably aspirin; the mechanism may involve inhibition of synthesis of bronchodilator prostaglandins, Other effects on the skin include photosensitivity, erythema multiforme, urticaria,

TABLE 15.2 Nonsteroidal anti-inflammatory drugs licenced in the UK

Chemical class	Generic name	Compound	Half-life ($t^{1}/_{2}$)	Usual adult dose
Para-amino phenol	paracetamol	acetaminophen	2 h	1 g qid
Salicylic acids	aspirin	acetylsalicylic acid	15 min	300–900 mg q.d.s. maximum 4 g daily
	diflusinal	salicylate	7–15 h	500–1000 mg daily in 1 or 2 doses
	benorilate	salicylate-paracetamol ester		1.5 g q.d.s.
Acetic acids	indometacin	indole	4 h	initially 50–75 mg daily as 1 or 2 doses, maximum 200 mg daily
	acemetacin	indole	3 h	60 mg b.d. or t.d.s.
	sulindac	indene	8 h	200 mg b.d.
	diclofenac sodium	phenylacetic acid	2 h	75–150 mg daily in 2 divided doses
	etodolac	pyranocarboxyate	7 h	600 mg o.d.
	ketorolac	ketorolac trometerol	5h	
Fenamic acid	mefanamic acid	fenamate	3 h	500 mg t.i.d.
Propionic acids	ibuprofen	propionic acid	2 h	1.6–2.4 g daily in divided doses
	fenbufen	propionic acid	10 h	300 mg in a.m. and 600 mg nocte, or 450 mg b.d.
	fenoprofen	propionic acid	3 h	300–600 mg t.d.s. or q.d.s., maximum 3 g daily
	flurbiprofen	propionic acid	4 h	150–200 mg daily in divided doses, maximum 300 mg daily
	ketoprofen	propionic acid	1 h	100–200 mg in 2–4 divided doses
	naproxen	propionic acid	14 h	250–500 mg b.d.
	tiaprofenic acid	propionic acid	2 h	600 mg in 2–3 divided doses
Enolic acids	piroxicam	oxicam	45 h	20 mg o.d.
	meloxicam	oxicam	20 h	7.5–15 mg o.d.
	tenoxicam	oxicam	72 h	20 mg o.d.
	azapropazone	benzotriazine	18 h	1.2 g daily in 2 or 4 divided doses
	phenylbutazone	pyrazone	72 h	
Non-acid drugs	nabumetone	napthylalkanone	22 h	1 g nocte, additional 500 mg — 1 g o.d. if necessary
	celecoxib	coxib	10 h	200–400 mg daily in divided doses
	aceclofenac	phenylacetoxyacetic acid	4 h	100 mg b.d.
	rofecoxib	coxib	17 h	12.5–25 mg o.d.

ANESTHESIA

The word anesthesia is derived from Greek language, the word "an" means without and the aisthetos means sensation. in which anesthesia means loss of all forms of sensation including pain touch, temperature and pressure perception and may be accompanied by impairment of motor function..

GENERAL ANESTHESIA

General anesthesia is a state of (CNS) depression, during which there is complete loss of sensation, consciousness, pain perception, and memory. It has three components: **hypnosis, analgesia, and muscle relaxation** Several different drugs are usually combined to produce desired levels of these components without excessive CNS depression. This so-called **Balanced surgical anesthesia (hypnosis with analgesia and muscular relaxation)** also allows lower dosages of potent general anesthetics.

STAGES OF GENERAL ANAESTHESIA

Surgical anesthesia is classically divided into four stages: **Analgesia, Excitement, Surgical anesthesia and Medullary paralysis (overdose)**.

ADJUFANT TO ANESTHESIA

Several non anesthetic drugs are used as adjuncts to anesthetic drugs. include **antianxiety** , **sedative-hypnotics** , **anticholinergics**, and **opioid analgesics, neuromuscular blocking agents.**

Before surgery (premedication)

Anxiolysis and amnesia. . Sedative premedication Benzodiazepines, provide anxiolysis and amnesia for the immediate presurgical period

Analgesia is indicated if the patient is in pain preoperatively or it can be given to prevent postoperative pain

Drying of bronchial and salivary secretions using antimuscarinic drugs .the antimuscarinic of choice for this purpose atropine and hyoscine

During surgery

The aim is to induce unconsciousness, analgesia and muscular relaxation. A typical general anesthetic consists of:

Induction:

1. Usually intravenous: small dose of an opioid, e.g., fentanyl to provide analgesia. and sedation, followed by propofol or, , thiopental or etomidate to induce anesthesia.
2. Inhalational induction, usually volatile agent e.g. sevoflurane,

• **Maintenance:**

1. Most commonly with nitrous oxide and oxygen or oxygen plus a volatile agent, e.g., isoflurane or sevoflurane. Additional doses of a neuromuscular blocker or opioid are given as required.
2. A continuous intravenous infusion of propofol can be used to maintain anesthesia

Inhalation anaesthetics

The preferred inhalation agents are that are minimally irritant and non flammable**, nitrous oxide** and the fluorinated hydrocarbonse **Halothane**, **Isoflurane** , **Sevoflurane**, **Enflurane** ,. **Desflurane**)

Intravenous anaesthetics

Propofol , Thiopental, Etomidate, Ketamine

Muscle relaxants (NEUROMUSCULAR BLOCKING DRUGS)

• used to provide muscular relaxation during surgery occasionally to assist mechanical ventilation in intensive therapy units.

• They are used during electroconvulsive therapy to prevent injury to the patient due to excessive muscular contraction

After surgery

Relief of pain

opioid provides excellent pain relief after major surgery such as laparotomy.like Parenteral morphine, The addition of regular paracetamol and a NSAID, will provide additional pain relief and reduce the requirement for morphine. NSAIDs are contraindicated if there is a history of gastrointestinal ulceration , renal blood flow is compromised

Local Anesthesia

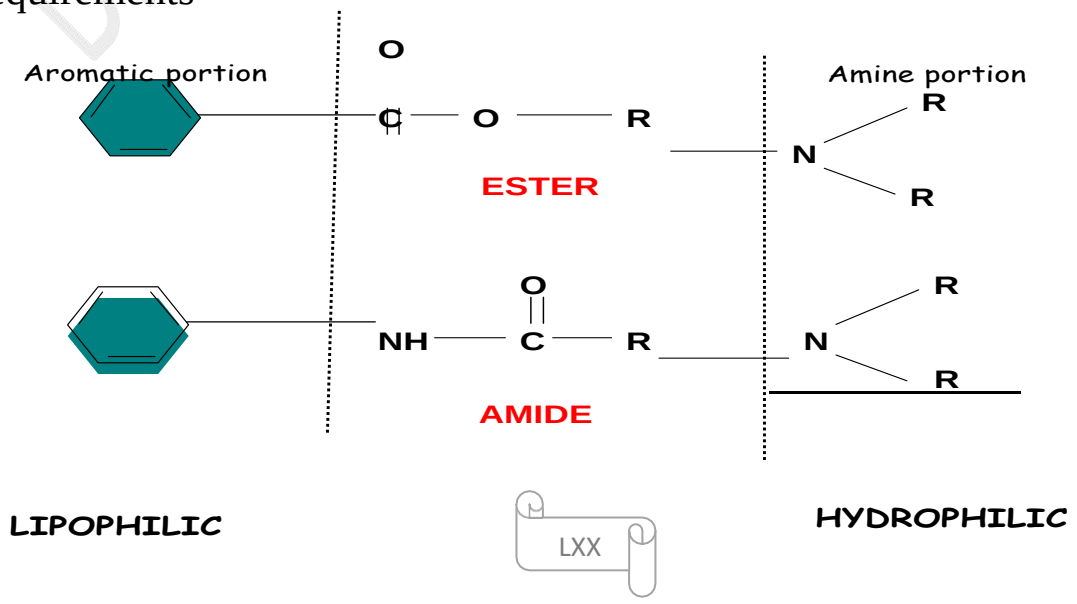
reversible loss of sensation in a limited area of the body caused by a depression of excitation in nerve ending or an inhibition of the conduction process in peripheral nerve

Mechanism of Action

The primary mechanism of action of local anesthetic is blockade voltage gated sodium channels. The excitable membrane of nerve axons maintains a resting transmembrane potential at -90 to -60mv; while during excitation, the sodium channels open and fast inward of sodium current quickly depolarized the membrane toward the sodium equilibrium potential +40mv. As result of this depolarization process the sodium channels closed and the potassium channels opened and the entrance of potassium repolarized the membrane to ward -95mv repolarization returns.

Chemistry of Local Anesthetics

The typical chemical structure of local anesthetic contains hydrophilic and lipophilic moieties that are separated by intermediate ester or amide linkage. These minimum structural features can satisfy the requirements



Clinical Effect and uses of Lidocaine

1. Local anesthetic effect
2. Cardiovascular effect lidocaine decrease electrical excitability of the myocardium, decrease conduction rate and decrease force of contraction which useful in hyperexitable myocardium in which lidocaine used in the management of ventricular tachycardia
3. Central Nervous System effect

A: Anticonvulsant effect which decrease the excitability of hyperexcitable cortical neurons which rise the seizure threshold

B: increase pain threshold and may produce degree of analgesia

. **Toxicity of Lidocaine**

1. C NS: Toxic doses of lidocaine first produce stimulation followed by depression vary from mild restlessness to severe convulsion.
2. CVS: It produced overall inhibition on the contractility of the heart muscle, decrease the electrical excitability of myocardium, decrease force of contraction, and decrease rate of electrical impulse conduction
3. Vasculature: vasodilatation by direct relaxing effect on smooth muscle of vessels walls which contribute to hypotension and cardiovascular collapse.
4. Respiratory system: Respiratory arrests are the most common cause of death related to over dose of lidocaine.
5. Neuro toxicity: Lidocaine when applied at excessively high concentration produces neuronal toxicity.

Availability of Lidocaine

Lidocaine available as 2% jelly form, 5% ointment, 10%,15% spray 2% dental cartridge with 1:80000 or 1:100000 or 1:200000 epinephrine,2% dental cartridge without epinephrine, 2% vial without epinephrine and 2% vial with epinephrine with different concentration.

Vasoconstrictors

. are the agents add to local anesthetic solutions to oppose vasodilatation and achieve hemostasis.

The addition of vasoconstrictors to local anesthetic agent causes

1. vasoconstriction which reduced blood flow to site of injection.
2. Decrease rate of absorption of local anesthetic into circulation.
3. Decrease plasma level of local anesthetic and decreasing the risk of systemic toxicity of local anesthetics.
4. Higher volume of local anesthetic remains in and around the nerve for longer periods, thereby increasing the duration of action of most local anesthetics.
5. It decreases bleeding at the site of injection because of decreased perfusion

DRUGS ACT ON RESPIRATORY SYSTEM

Asthma

Asthma is an airway disorder characterized by bronchoconstriction, inflammation and hyperreactivity to various stimuli. Resultant symptoms include dyspnea, wheezing, chest tightness, cough, and sputum production..

Acute symptoms of asthma may be precipitated by numerous stimuli, may initiate both inflammation and bronchoconstriction. Viral infections of the respiratory tract are often the causative agents, especially in infants and young children whose airways are small and easily obstructed. Asthma symptoms may persist for days or weeks after the viral infection resolves.

In about 25% of patients with asthma, aspirin and other (NSAIDs) can precipitate an attack. Some patients are allergic to sulfites and may experience life-threatening asthma attacks if they ingest foods processed with these preservatives (eg, beer, wine, dried fruit)..

Gastro esophageal reflux disease (GERD), a common disorder characterized by heartburn and esophagitis, is also associated with asthma. Asthma that worsens at night may be associated with nighttime acid reflux. (Asthma may also aggravate GERD, because antiasthma medications that dilate the airways also relax muscle tone in the gastro esophageal sphincter and may increase acid reflux.)

Bronchodilators

Adrenergics: Adrenergic drugs stimulate beta2-adrenergic receptors in the smooth muscle of bronchi and bronchioles. . Some beta-adrenergic drugs also stimulate beta1-adrenergic receptors in the heart to increase the rate and force of contraction. Cardiac stimulation is an adverse effect when the drugs are given for bronchodilator.

Epinephrine may be injected subcutaneously in acute attack bronchoconstriction,. However, an inhaled selective beta2 agonist is the drug of choice in this situation.

Salbutamol (Albuterol) short-acting beta2-adrenergic agonists used for prevention and treatment of bronchoconstriction. act more selectively on beta2 receptors and cause less cardiac stimulation than epinephrine. Most often taken by inhalation, they are also the most effective bronchodilators and the treatment of first choice to relieve acute asthma.

Terbutaline is a relatively selective beta2-adrenergic agonist that is a long-acting bronchodilator. Muscle tremor is the most frequent side effect with this agent.

Anticholinergics

Anticholinergics block the action of acetylcholine in bronchial smooth muscle. **Ipratropium** was formulated to be taken by inhalation for maintenance therapy of bronchoconstriction associated with chronic bronchitis and emphysema. Improved pulmonary function usually occurs in a few minutes. Ipratropium cautious use is recommended in patients with narrow-angle glaucoma and prostatic hypertrophy.

Xanthines

The main xanthine used clinically is **theophylline**.. producing to bronchodilation, , decreasing vascular permeability, increasing the ability of cilia to clear mucus from the airways, . Theophylline also increases cardiac output, causes peripheral vasodilation, exerts a mild diuretic effect, and stimulates the CNS.

Anti-inflammatory Agents

Corticosteroids are used in the treatment of acute and chronic asthma and other bronchoconstrictive disorders,

Beclomethasone, budesonide, flunisolide, fluticasone, and **triamcinolone** are topical corticosteroids for inhalation. Topical administration minimizes systemic absorption and adverse effects.

Hydrocortisone, prednisone, and **methylprednisolone** are given to patient who require systemic corticosteroids. Prednisone is given orally; hydrocortisone and methylprednisolone may be given IV to patients who are unable to take an oral medication.

Mast Cell Stabilizers

Cromolyn and **nedocromil** stabilize mast cells and prevent the release of bronchoconstrictive and inflammatory substances when mast cells are confronted with allergens and other stimuli. The drugs are indicated only for prophylaxis of acute asthma attacks in clients with chronic asthma.

Antiasthmatic Drugs

1. A selective, short-acting, inhaled beta2-adrenergic agonist (eg, sabutamol) is the initial drug of choice for acute bronchospasm. . drugs given by inhalation can usually be given in smaller doses and produce fewer adverse effects than oral or parenteral drugs.

2. Ipratropium, the anticholinergic bronchodilator, is most useful in the long-term management of COPD. It is ineffective in relieving acute bronchospasm by itself, but it adds to the bronchodilating effects of adrenergic drugs.

3. Theophylline less used now considered a second-line drug

4. Cromolyn and nedocromil are used prophylactically; they are ineffective in acute bronchospasm.

5. Because inflammation has been established as a major component of asthma, an inhaled corticosteroid is being used often given orally or IV for several days.common regimen for treatment of moderate asthma

ANTIHISTAMINES

Mechanism of Action

Antihistamines are structurally related to histamine and occupy the same receptor sites as histamine, which prevents histamine from acting on target tissues Thus, the drugs are effective in inhibiting vascular permeability, edema formation, bronchoconstriction, and pruritus associated with histamine release. They do not prevent histamine release or reduce the amount released.

First-Generation H1 Receptor Antagonists

These chemically diverse antihistamines (also called nonselective or sedating agents) bind to both central and peripheral H1 receptors and can cause CNS depression (drowsiness ,sedation) They also have substantial anticholinergic effects (eg, cause dry mouth, urinary retention, constipation, blurred vision). **Dexchlorpheniramine (Polaramine)** cause minimal drowsiness. **Diphenhydramine (Allermine),** the prototype of first-generation antihistamines, causes a high incidence of drowsiness and anticholinergic effects.

Second-Generation H1 Receptor Antagonists

Second-generation H1 antagonists (also called selective or non sedating agents) were developed mainly to produce less sedation than the first-generation drugs. They cause less CNS depression because they are selective for peripheral H1 receptors and do not cross the blood–brain barrier. **Azelastine (Astelin)** is the only antihistamine formulated as a nasal spray **Cetirizine . Fexofenadine.Loratadine .Desloratadine**

Indications for Use

Antihistamines are used for a variety of allergic and nonallergicdisorders

Allergic rhinitis

- **Anaphylaxis.**.
- **Allergic conjunctivitis.**
- **Drug allergies and pseudoallergies.**
- **Transfusions of blood and blood products.**
- **Dermatologic conditions.**.

- **Miscellaneous.** Some antihistamines are commonly used for nonallergic disorders, such as motion sickness, nausea and vomiting (eg, promethazine, hydroxyzine; and sleep (eg, diphenhydramine). The active ingredient in OTC sleep aids is a sedating antihistamine.

Contraindications to Use

Antihistamines are contraindicated or must be used with caution in clients with hypersensitivity to the drugs, narrow angle glaucoma, prostatic hypertrophy, and bladder neck obstruction, and during pregnancy

Cough

• **Cough** is a forceful expulsion of air from the lungs. It is normally a protective reflex for removing foreign bodies, environmental irritants, or accumulated secretions from the respiratory tract.

The cough reflex involves central and peripheral mechanisms.

Centrally, the cough center in the medulla oblongata receives stimuli and initiates the reflex response

Peripherally, cough receptors in the pharynx, larynx, trachea, or lungs may be stimulated by air, dryness of mucous membranes, or excessive secretions.

There are two type of cough: the useful and the useless.

Cough is useful when it effectively expels secretions or foreign material from the respiratory tract, i.e. when it is *productive;* it is useless when it is unproductive and persistent.

Useful cough should be allowed to serve its purpose and suppressed only when it is exhausting the patient or is dangerous ,e.g. after surgery. Useless persistent cough should be stopped..

COUGH SUPPRESSION

Antitussives that act centrally

The most consistent means of suppressing cough is blockade of the medullary cough centre itself. Opioids, such as codeine, are very effective antitussive ..There are also nonopioid antitussive **dextromethorphan** . have no significant analgesic or respiratory depressant effects at the doses required for their antitussive action .

Locally acting agents (eg, throat lozenges, cough drops) may suppress cough by increasing the flow of saliva and by containing demulcents or local anesthetics to decrease irritation of pharyngeal mucosa. Flavored syrups are often used as vehicles for other drugs.

The major clinical indication of antitussives is a dry , , nonproductive cough that interferes with rest and sleep. It is not desirable to suppress a productive cough because the secretions need to be removed.

Expectorants

Expectorants are agents given orally to liquefy respiratory secretions and allow for their easier removal. Guaifenesin (glyceryl guaiacolate)is the most commonly used expectorant. It is available alone and as an ingredient in many combination cough and cold remedies,

Mucolytics

Mucolytics are administered to liquefy mucus in the respiratory tract.Acetylcysteine is effective within 1 minute after inhalation.

Cold Remedies

Many combination products are available for treating symptoms of the common cold. Many of the products contain an antihistamine, a nasal decongestant, and an analgesic. Some contain antitussives, expectorants, and other agents as well. Many cold remedies are over-the-counter (OTC) formulations. Commonly used ingredients include chlorpheniramine (antihistamine), pseudoephedrine (adrenergic nasal decongestant), acetaminophen (analgesic and antipyretic), dextromethorphan (antitussive), and guaifenesin (expectorant).

Drugs act on GIT

ANTACIDS

weak bases that react with gastric HCL to form a salt and water. After meal, approximately 45 mEq/h of HCL secreted. A single dose of 156 mEq of antacid given 1 hour after a meal effectively neutralizes gastric acid for up to 2 hours, have been used in the treatment of patients. With intermittent heartburn and dyspepsia and acid-peptic disorders .

Sodium bicarbonate reacts rapidly with HCl to produce carbon dioxide and NaCl, Sodium chloride absorption may exacerbate fluid retention in patients with heart failure, hypertension, and renal insufficiency.

Calcium carbonate is less soluble and reacts more slowly than sodium bicarbonate with HCl to form carbon dioxide and CaCl2. Excessive doses calcium carbonate with calcium-containing dairy products can lead to hypercalcemia, renal insufficiency, and metabolic alkalosis (milk-alkali syndrome).

Formulations(magnesium hydroxide or aluminum hydroxide) react slowly with HCl to form magnesium chloride or aluminum chloride and water. no gas is generated,. Because unabsorbed magnesium salts may cause an osmotic diarrhea and aluminum salts may cause constipation, these agents are commonly administered together in proprietary formulations (eg, Gelusil, Maalox) to minimize the impact upon bowel function. Both magnesium and aluminum are absorbed and excreted by the kidneys. Hence, patients with renal insufficiency should not take these agents long-term.

Drugs Used In Acid-Peptic Diseases

Acid-peptic diseases include gastro esophageal reflux, peptic ulcer (gastric and duodenal), and stress-related mucosal injury. In all these conditions, mucosal erosions or ulceration arise when the caustic effects of aggressive factors (acid, pepsin, bile) overwhelm the defensive factors of the gastrointestinal mucosa (mucus and bicarbonate secretion, prostaglandins, blood flow, and the processes of restitution and regeneration after cellular injury).

Agents That Reduce Intragastric Acidity

1- ANTACIDS

2-H2-RECEPTOR ANTAGONISTS

Four H2 antagonists are in clinical use:

Cimetidine , Ranitidine, Famotidine, and Nizatidine

The H2 antagonists exhibit competitive inhibition at the parietal cell and suppress basal and meal-stimulated acid secretion in a linear, dose-dependent manner

Clinical Uses

A. Gastroesophageal Reflux Disease (Gerd)

B. Peptic Ulcer Disease

C. Nonulcer Dyspepsia

D. Prevention Of Bleeding From Stress-Related Gastritis

Adverse Effects

H2 antagonists are extremely safe drugs. Adverse effects occur in fewer than 3% of patients and include diarrhea, headache, fatigue, myalgias, and constipation.

Cimetidine inhibits binding of dihydrotestosterone to androgen receptors, inhibits metabolism of estradiol, and increases serum prolactin levels. When used long-term or in high doses, it may cause gynecomastia or impotence in men and galactorrhea in women.

PREGNANCY AND NURSING MOTHERS

they should not be administered to pregnant women unless absolutely necessary. The H2 antagonists are secreted into breast milk and may therefore affect nursing infants.

Drug Interactions

Cimetidine interferes with several important hepatic cytochrome P450 drug metabolism pathways. Ranitidine binds 4-10 times less than cimetidine to cytochrome P450. Negligible interaction occurs with nizatidine and famotidine

3-PROTON PUMP INHIBITORS (PPI)

Five proton pump inhibitors are available for clinical use

Omeprazole

Lansoprazole

Rabeprazole

Pantoprazole

Esomeprazole

In contrast to H2 antagonists, proton pump inhibitors inhibit both fasting and meal-stimulated secretion because they block the final common pathway of acid secretion

Clinical Uses

A. Gastroesophageal Reflux Disease (Gerd)

B. Peptic Ulcer Disease

C. NSAID- Associated Ulcers

D. Nonulcer Dyspepsia.

MUCOSAL PROTECTIVE AGENTS

Sucralfate

Prostaglandin Analogs

Misoprostol has both Acid Inhibitory And Mucosal Protective Properties**..**

Colloidal Bismuth Compounds

Antispasmodics (Anticholinergics)

Agents are promoted as providing relief of abdominal pain or discomfort through antispasmodic actions.

These agents work primarily through anticholinergic activities. Commonly used medications in this class include hyoscyamine. These drugs inhibit muscarinic cholinergic receptors in the enteric plexus and on smooth muscle.

At low doses, they have minimal autonomic effects.

However, at higher doses they exhibit significant additional anticholinergic effects, including dry mouth, visual disturbances, urinary retention, and constipation.

ANTI EMETIC

Nausea and vomiting may be manifestations of a wide variety of conditions(adverse effects from medications; systemic disorders or infections; pregnancy; vestibular dysfunction; CNS infection or increased pressure; peritonitis; hepatobiliary disorders; radiation or chemotherapy; and gastrointestinal obstruction, dysmotility, or infections

Metoclopramide and domperidone are dopamine D2 receptor antagonists.. These agents increase esophageal peristaltic amplitude, increase lower esophageal sphincter pressure, and enhance gastric emptying. Metoclopramide and domperidone also block dopamine D2 receptors in the chemoreceptor trigger zone of the medulla, resulting in potent antinausea and antiemetic action.

Clinical Uses

A. Gastroesophageal Reflux Disease (Gerd)

B. Impaired Gastric Emptying

C. Nonulcer Dyspepsia.

D. Prevention Of Vomiting

E. Postpartum Lactation Stimulation

Adverse Effects

The most common adverse effects of metoclopramide involve the Restlessness, drowsiness, insomnia, anxiety, and agitation occur especially the elderly Elevated prolactin levels can cause galactorrhea,gynecomastia, impotence, and menstrual disorders.

LAXATIVES

Bulk-Forming Laxatives indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis. Common preparations include natural plant products (, methylcellulose) and synthetic fibers

Stool Surfactant Agents (Softeners) These agents soften stool material, permitting water and lipids to penetrate.. Common agents include glycerin suppository..

Osmotic Laxatives :Non absorbable Sugars or Salts

These agents may be used for the treatment of acute constipation or the prevention of chronic constipation. The commonly purgatives are magnesium citrate and sodium phosphate.

Stimulant Laxatives(Cathartic).

Stimulant laxatives (cathartics) induce bowel movements through a number of poorly understood mechanisms.

Anthraquinone Derivatives Aloe, senna, and cascara occur naturally in plants. These laxatives are poorly absorbed and after hydrolysis in the colon, produce a bowel movement

Castor Oil Formerly used as a purgative to clean the colon before procedures, it is now seldom used.

Biscodel stimulated bowel

Antidiarrheal Agents

Antidiarrheal agents may be used safely in patients with mild to moderate acute diarrhea. However, they should not be used in patients with bloody diarrhea, high fever, or systemic toxicity because of the risk of worsening the underlying condition.. Antidiarrheals are also used to control chronic diarrhea caused by such conditions as irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD).

Opioids

have significant constipating effects (increased colonic transit time and fecal water absorption. They also decrease mass colonic movements and the gastrocolic reflex.**Loperamide** is a nonprescription opioid agonist that does not cross the blood-brain barrier and has no analgesic properties or potential for addiction.

. Commercial preparations commonly contain small amounts of atropine to discourage overdosage (2.5 mg diphenoxylate with 0.025 mg atropine). The anticholinergic properties of atropine may contribute to the antidiarrheal action.

Colloidal Bismuth Compounds

Kaolin is a naturally occurring hydrated magnesium aluminum silicate, and **pectin** is an indigestible carbohydrate derived from apples. Both appear to act as absorbents of bacteria, toxins, and fluid, thereby decreasing stool liquidity and number.

The Treatment Of Irritable Bowel Syndrome.

Irritable bowel syndrome (IBS) is an idiopathic chronic, relapsing disorder characterized by abdominal discomfort (pain, bloating, distention, or cramps) in association with alterations in bowel habits (diarrhea, constipation, or both)

Pharmacologic therapies directed at relieving abdominal pain and discomfort and improving bowel function.For the treatment of chronic abdominal pain, low doses of tricyclic antidepressants (eg, amitriptyline or desipramine, appear to be helpful . The anticholinergic properties of these agents also may have effects on gastrointestinal motility and secretion, reducing stool frequency and liquidity of stools

Drugs Treat Inflammatorybowel Disease

Inflammatory bowel disease (IBD) comprises two distinct disorders: ulcerative colitis and Crohn's disease.

1- Aminosalicylates

Drugs that contain 5-aminosalicylic acid (5-ASA) have been used successfully for decades in the treatment of inflammatory bowel diseases.

A. Azo Compounds Sulfasalazine, balsalazide, and olsalazine

B. Mesalamine Compounds

2- Purine Analogs: Azathioprine & 6-Mercaptopurine

3- Methotrexate

DRUGS ACT ON RENAL SYSTEM

RENAL PHYSIOLOGY

The primary function of the kidneys is to regulate the volume, composition, and pH of body fluids. The kidneys receive approximately 25% of the cardiac output. From this large amount of blood flow, the normally functioning kidney is efficient in retaining substances needed by the body and eliminating those not needed.

The nephron is the functional unit of the kidney; each kidney contains approximately 1 million nephrons. Each nephron is composed of a glomerulus and a tubule

The glomerulus is a network of capillaries that receives blood from the renal artery. Bowman‘s capsule is a thin-walled structure that surrounds the glomerulus, then narrows and continues as the tubule.

The tubule is a thin walled structure of epithelial cells surrounded by peritubular capillaries. The tubule is divided into main segments, the proximal tubule, loop of Henle, and distal tubule, which differ in structure and function

The nephron functions by three processes:

Glomerular filtration,

Tubular reabsorption

Tubular secretion.

These processes normally maintain the fluid volume, electrolyte concentration, and pH of body fluids within a relatively narrow range. They also remove waste products of cellular metabolism. A minimum daily urine output of approximately 400 mL is required to remove normal amounts of metabolic end products.

Glomerular Filtration

Arterial blood enters the glomerulus by the afferent arteriole at the relatively high pressure of approximately 70 mm Hg.This pressure pushes water, electrolytes, and other solutes outof the capillaries into Bowman‘s capsule and then to the proximal tubule. This fluid, called glomerular filtrate, contains the same components as blood except for blood cells, fats, and proteins that are too large to be filtered. The glomerular filtration rate (GFR) is about 180 L/day, or 125 mL/minute.

Tubular Reabsorption

The term reabsorption, in relation to renal function, indicates movement of substances from the tubule (glomerular filtrate) to the blood in the peritubular capillaries.

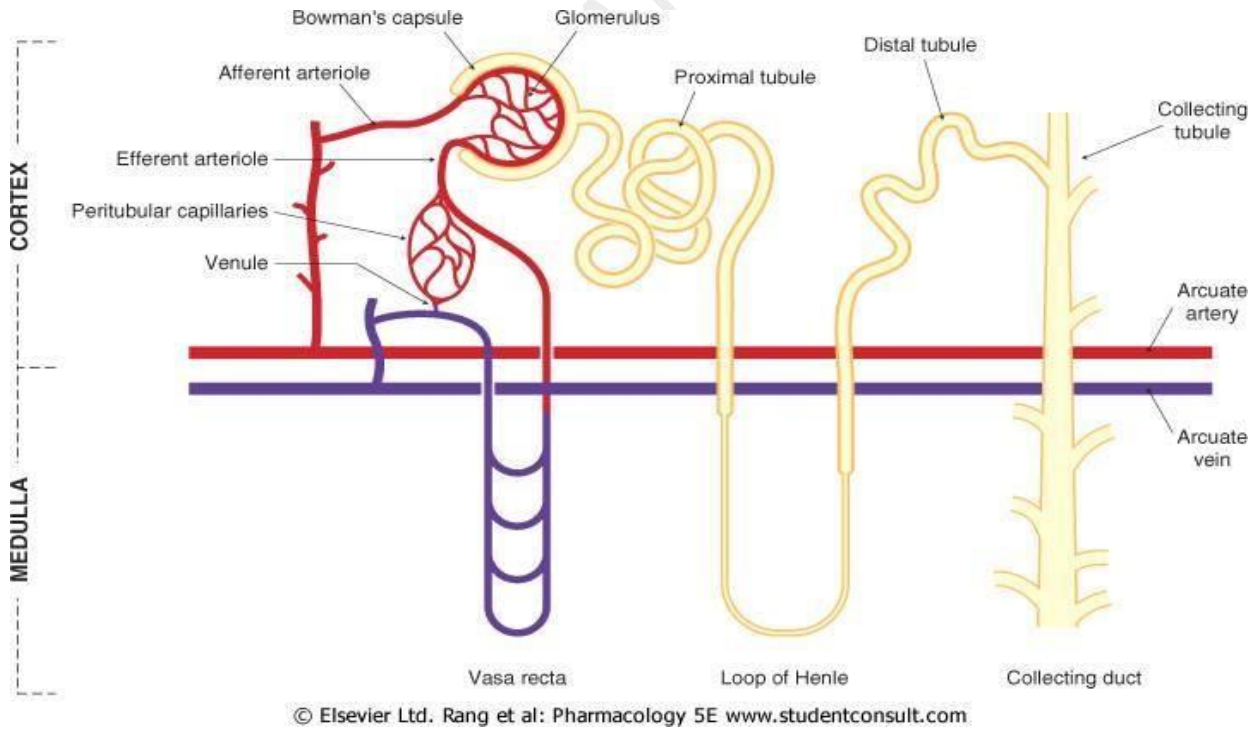
Most reabsorption occurs in the proximal tubule, The remaining water and solutes are now called urine

Antidiuretic hormone from the posterior pituitary gland promotes reabsorption of water from the distal tubules and the collecting ducts of the kidneys. This conserves water needed by the body and produces more concentrated urine. Aldosterone, a hormone from the adrenal cortex, promotes sodium–potassium exchange mainly in the distal tubule and collecting ducts. Thus, aldosterone promotes sodium reabsorption and potassium loss.

Tubular Secretion

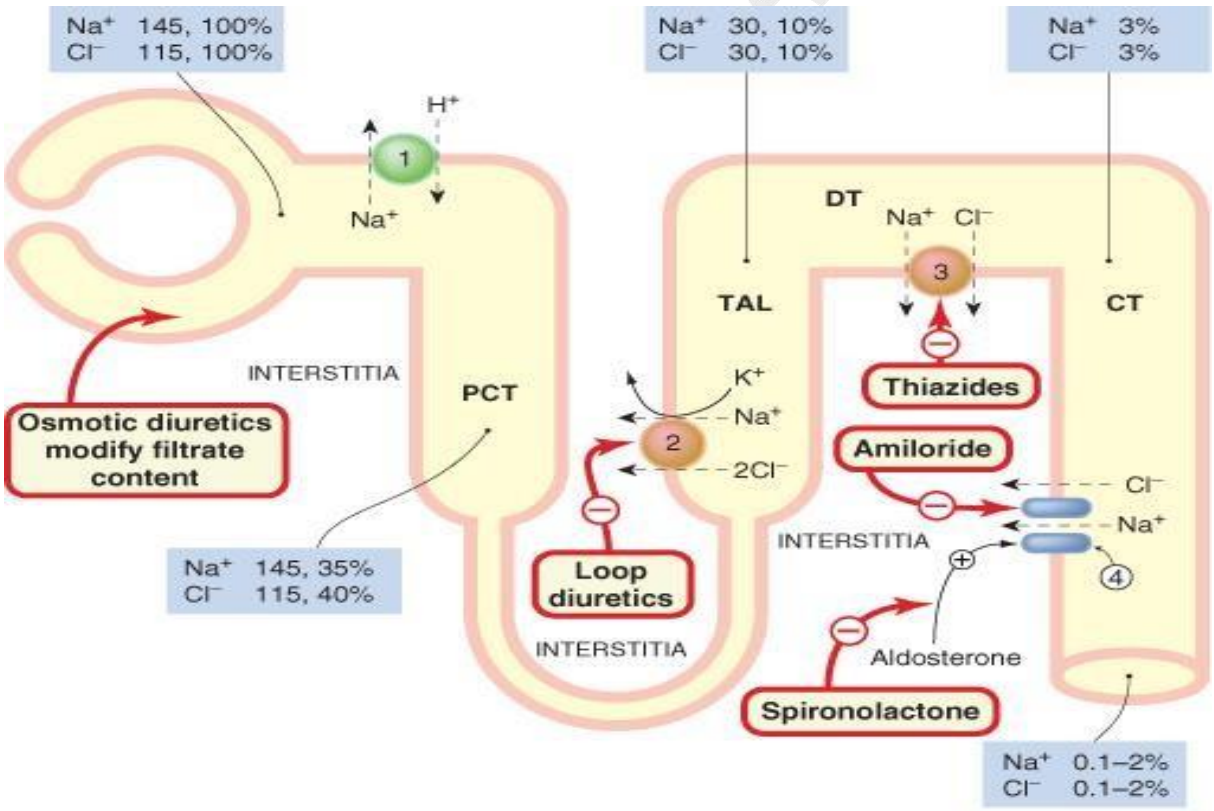
The term secretion, in relation to renal function, indicates movement of substances from blood in the peritubular capillaries to glomerular filtrate flowing through the renal tubules Secretion occurs in the proximal and distal tubules, across the epithelial cells that line the tubules. In the proximal tubule, uric acid, creatinine, hydrogen ions, and ammonia

are secreted; in the distal tubule, potassium ions, hydrogen ions, and ammonia are secreted. Secretion of hydrogen ions is important in maintaining acid–base balance in body fluids.



Diuretics

Diuretics are drugs that increase renal excretion of water, sodium, and other electrolytes, thereby increasing urine formation and output. They are important therapeutic agents widely used in the management of edematous (e.g., heart failure, renal and hepatic disease) and nonedematous (e.g., hypertension, ophthalmic surgery) . Diuretics are also useful in preventing renal failure by their ability to sustain urine flow



Major subclasses of diuretics

Loop Diuretics

Loop diuretics inhibit sodium and chloride reabsorption in the ascending limb of the loop of Henle, where reabsorption of most filtered sodium occurs.

Thus, these potent drugs produce significant diuresis, with their sodium-losing effect up to 10 times greater than that of thiazide diuretics. are the most effective diuretics available for clinical use.

Loop diuretics may be given orally or IV.

Loop diuretics are the diuretics of choice when rapid effects are required (eg, in pulmonary edema) and when renal function is impaired. The drugs are contraindicated during pregnancy unless absolutelynecessary.

Furosemide is the most commonly used loop diuretic

Bumetanide may be used to produce diuresis in some clients who are allergic to or no longer respond to furosemide.

Thiazide And Thiazide Related Diuretics

Thiazide diuretics are synthetic drugs that are chemically related to the sulfonamides and differ mainly in their duration of action.
They act to decrease reabsorption of sodium, water, chloride, and bicarbonate in the distal convoluted tubule.

Most sodium is reabsorbed before it reaches the distal convoluted tubule and only a small amount is reabsorbed at this site. Thus, these drugs are not strong diuretics. In addition, they are ineffective when immediate diuresis is required and relatively ineffectivewith decreased renal function. They work efficiently only when urine flow is adequate. Hydrochlorothiazide is the most commonly used;

chlorothiazide is the only one that can be given IV.
Related diuretics are nonthiazides whose pharmacologic actions are essentially the same as those of the thiazides; they include **chlorthalidone, metolazone, and quinethazone**.

Thiazides and related diuretics are frequently prescribed in the long-term management of heart failure and hypertension.
Thiazides and related drugs are contraindicated in patient allergic to sulfonamide drugs. They must be used cautiously during pregnancy because they cross the placenta and may have adverse effects on the fetus by compromising placental perfusion.

Potassium-Sparing Diuretics

Sodium is normally reabsorbed in the distal tubule in exchange for potassium and hydrogen ions. Potassium-sparing diuretics act at the distal tubule to decrease sodium reabsorption and potassium excretion. This group includes **spironolactone, , amiloride and triamterene,** Potassium-sparing diuretics are weak diuretics when used alone. Thus, they are usually given in combination with potassium-losing diuretics to increase diuretic activity and decrease potassium loss.

Osmotic Diuretics

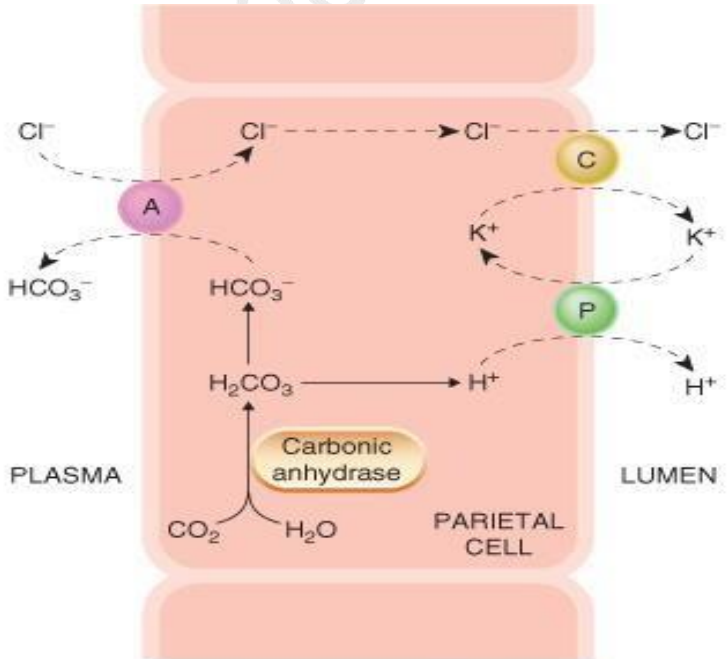
produce rapid diuresis by increasing the solute load (osmotic pressure) of the glomerular filtrate. The increased osmotic pressure causes water to be pulled from extravascular sites into the bloodstream

Mannitol is useful in managing oliguria or anuria, and it may prevent acute renal failure during prolonged surgery, trauma, Other important clinical uses of hyperosmolar agents include reduction of intracranial pressure before or after neurosurgery, reduction of intraocular pressure before certain types of ophthalmic surgery, and urinary excretion of toxic substances.

Carbonic anhydrase inhibitors

The enzyme carbonic anhydrase facilitates the reaction between carbon dioxide and water to form carbonic acid, which then breaks down to hydrogen(H+) and bicarbonate (HCO3 -) ions. This process fundamental to the production of either acid or alkaline secretions and high conc. of carbonic anhydrase are present in the gastric mucosa, pancreas, eye and kidney. Because the number of H+ available to exchange with Na+ in the proximal tubule is reduced, sodium loss and diuresis occur.

Acetazolamide is the most widely used carbonic anhydrase inhibitor. Reduction of intraocular pressure., acetazolamide can be taken either orally, or intravenously Acetazolamide is not recommended for long-term use because of the risk of hypokalaemia and acidosis, **dorzolamide** are effective as eye drops, well tolerated, and thus suitable for chronic use in glaucoma



DRUGS ACT ON CARDIO VASCULAR SYSTEM

HEART

The heart is a hollow, muscular organ that functions as a two sided pump to circulate five to six liters of blood through the body every minute.

Heart failure (HF), also called congestive heart failure (CHF)is a common condition that occurs when the heart cannot pump enough blood to meet tissue needs for oxygen and nutrients.

CARDIAC GLYCOSIDE

Digoxin (Lanoxin) exerts a cardio tonic effect that improves the pumping ability of the heart. Increased myocardial contractility allows the ventricles to empty more completely with each heartbeat.

The clinical uses of digoxin are management of HF, atrial fibrillation,and atrial flutter. Digoxin may be used in acute or chronic conditions, and maintenance therapy.

ATHEROSCLEROSIS

is a lesions in the endothelial lining of arteries. As the lesions develop and enlarge, they project into the lumen of the artery, reduce the size of the lumen, reduce blood flow, leads to damage of tissue supplied by the artery. Atherosclerosis is a major cause of angina pectoris, myocardial infarction heart failure, stroke, peripheral vascular disease, and death.

Drug Therapy Of Dyslipidemia

Dyslipidemic drugs are used to decrease blood lipids, to prevent or delay the development of atherosclerotic plaque The drugs act by altering the production, metabolism, or removal of lipids. Drug therapy is recommended when approximately 6 months of dietary lifestyle changes fail to decrease dyslipidemia to acceptable level.

Dyslipidemic Agents.

Statins

inhibit an enzyme (hydroxymethylglutaryl-coenzyme A reductase) required for hepatic synthesis of cholesterol

Rosivastatin Atorvastatin Fluvastatin Simvastatin

Fibrates: The drugs increase the oxidation of fatty acids in liver and muscletissue and thereby decrease hepatic production of triglycerides**,**

Fenofibrate Gemfibrozil

Angina

is chest pain that occurs because heart is not getting enough blood and oxygen.

Organic nitrate

act in the endothelial smooth muscle cell of blood vessels releases nitric oxide (NO), which is the main physiological vasodilator, normally produced by endothelial cells.

Glyceryl trinitrate (nitroglycerinGTN) Isosorbide dinitrate

Isosorbide mononitrate

Direct vasodilators

Hydralazine minoxidil Sodium nitroprusside

Dysrhythmias.

(arrhythmias) are abnormalities in heart rate or rhythm. They become significant when they interfere with cardiac function and ability to perfuse body tissues. Antidysrhythmic agents are diverse drugs used for prevention and management of cardiac dysrhythmias

CLASSIFICATIONS AND INDIVIDUAL DRUGS

Class I Sodium Channel Blockers

Class IA Quinidine,. Disopyramide Procainamide

Class IB Lidocaine, Mexiletine and Phenytoin,

Class IC Flecainide and propafenone

Class II Beta-Adrenergic Blockers: Esmolol,. Propranolol,.. Sotalol

Class III Potassium Channel Blockers amiodarone

Class IV Calcium Channel Blockers Diltiazem and verapamil

Hypertension

Is persistently high blood pressure that results from abnormalities in regulatory mechanisms. It is usually defined as a systolic pressure above 140 mm Hg or a diastolic pressure above 90 mm Hg on multiple blood pressure measurements.

Primary or essential hypertension (that no cause can be found)

Secondary hypertension (may from renal, endocrine, CNS disorders)

Hypertension , coronary heart disease (CHD) are of great importance.

Hypertension affects above 20% of the total population of the would with its major impact on those over age 50. CHD is the cause of death in 30% of males and 22% of females ,. Management requires attention to, dietary ,clinical and pharmacological detail

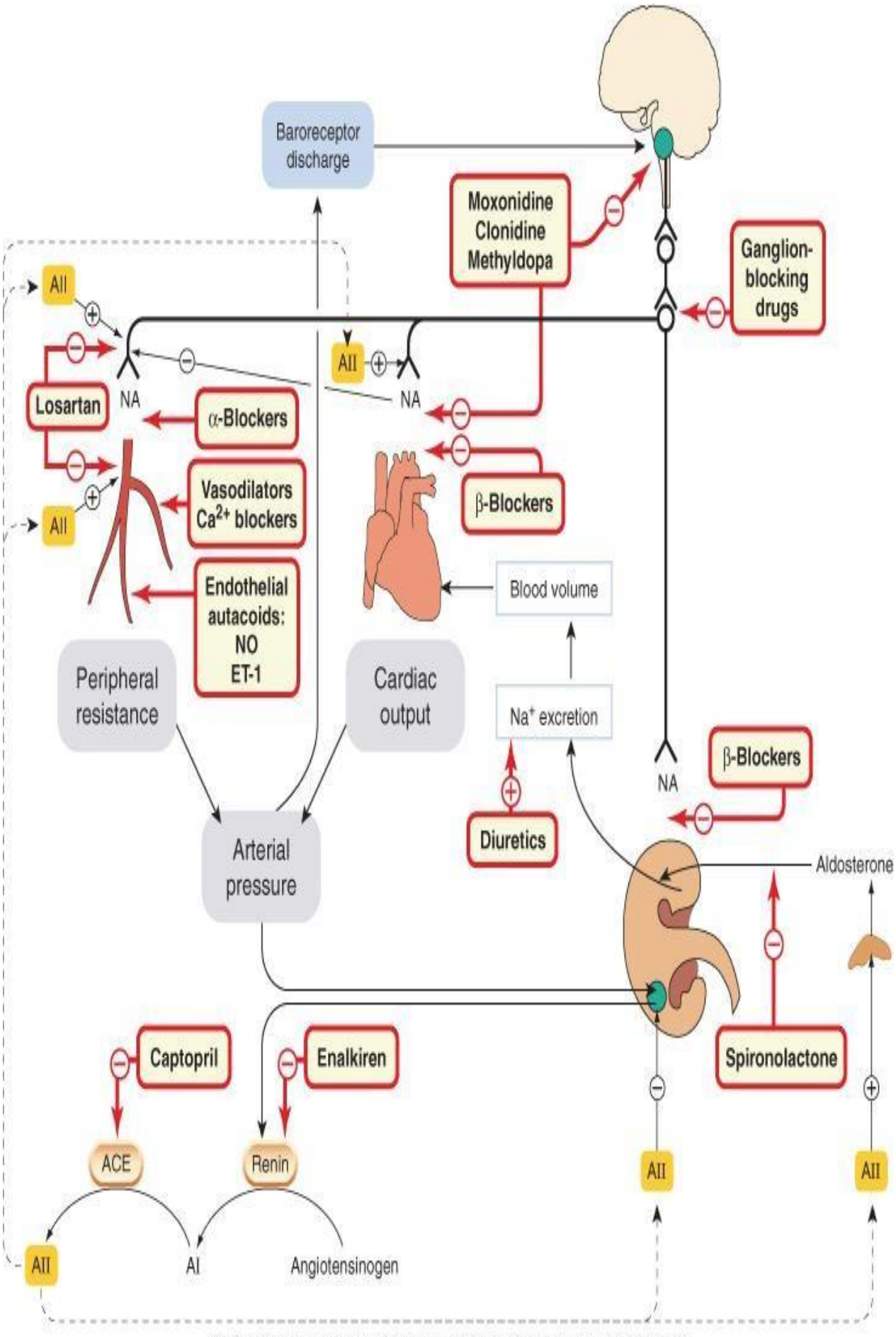
Hypertension: how drugs act

Consider the following relationship:

Blood pressure = cardiac output x peripheral resistance

Therefore drugs can lower blood pressure by:

• Dilatation of arteriolar resistance vessels.
Dilatation can be achieved through direct relaxation of vascular smooth muscle cells, by stimulation of nitric oxide (NO) production, or by blocking (suppressing) endogenous vasconstrictors, noradrenaline (norepinephrine) and angiotensin.
• Dilatation of venous capacitance vessels; reduced venous return to the heart (preload) leads to reduced cardiac output, especially in the upright position
• Reduction of cardiac contractility and heart rate.
• Depletion of body sodium. This reduces plasma volume,



ANTIHYPERTENSIVE DRUGS

1- **Diuretics,** Thiazide diuretics (eg, hydrochlorothiazide) are most commonly used in the management of hypertension. Loop diuretics (eg, furosemide) or potassium-sparing diuretics (eg, spironolactone) may be useful in some circumstances.

2- Vasodilators

3- Calcium channel blockers

Contraction of vascular smooth muscle cells requires an influx of calcium through calcium channels ,Calcium channel blockers inhibit the passage of calcium through the voltage dependent Calcium channels.

There are three structurally distinct classes of calcium channel blocker:

- Dihydropyridines (the most numerous)
- Phenylalkylamines (principally verapamil)
- Benzothiazepine (diltiazem).

Indications for use

- **Hypertension: amlodipine, nifedipine, verapamil**
- **Angina: amlodipine, diltiazem, nifedipine, verapamil**
- **Cardiac arrhythmia: verapamil**
- **Prevention of ischaemic neurological damage following subarachnoid haemorrhage: nimodip**ine

4- **Antiadrenergics**,

Beta-adrenergic blocking agents

Non selective :

Oxprenolol, Propranolol, Pindolol,Sotalol, Timolol , Nadolol

Selective :

Esmolol, Atenolol, Bisoprolol, Metoprolol, Nebivolol, Betaxolol

Non selectiv**e** Beta**,** alpha blockers (**- Carvedilol Labetalol)**

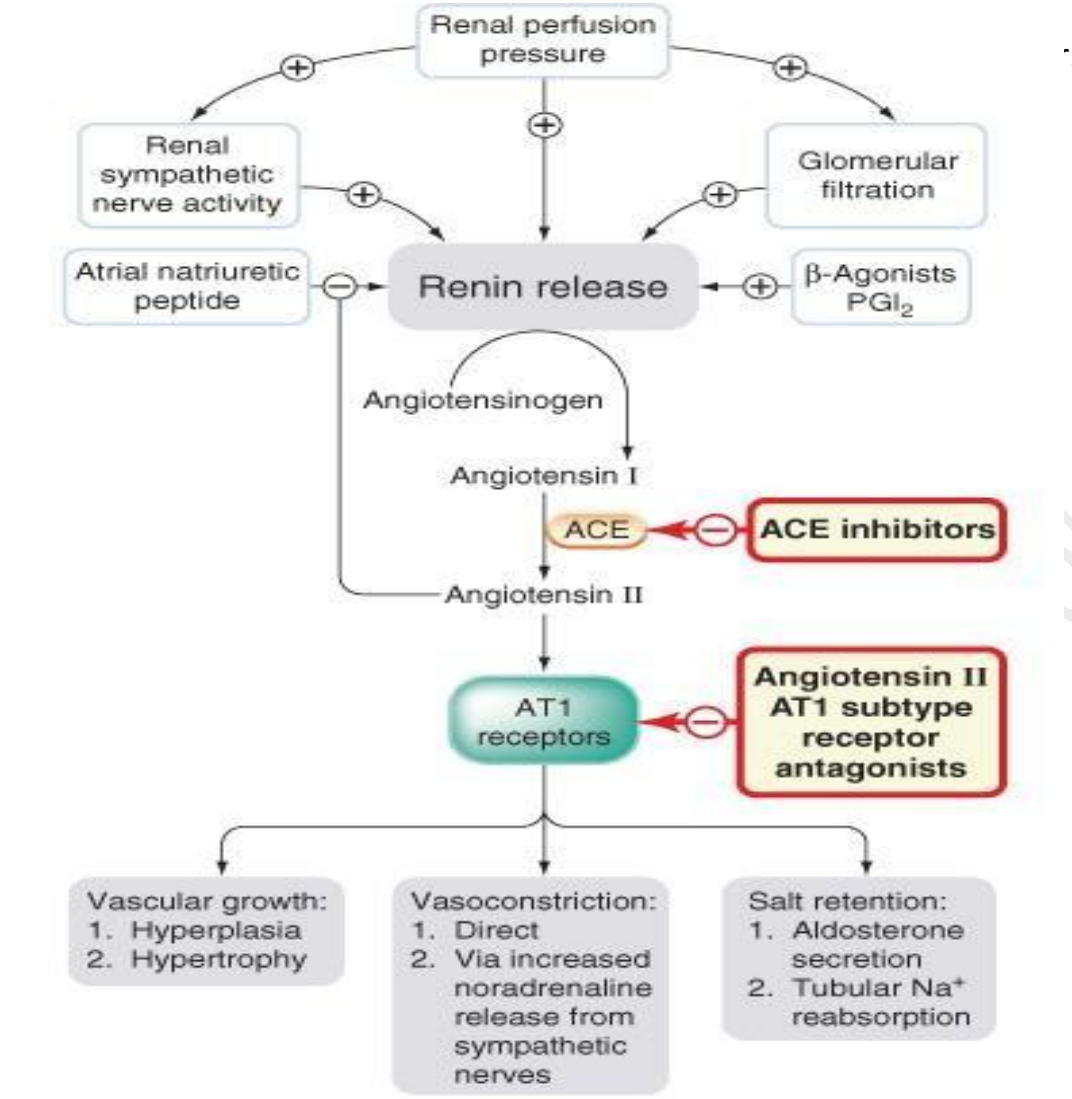
Alpha blockers (Phentolamine and Phenoxybenzamine),

5- Angiotensin-converting enzyme (ACE) inhibitors

(Captopril, Enalapril, Fosinopril, Lisinopril, Ramipril, Quinapril)

Angiotensin II receptor blockers(ARBs), also called angiotensin II receptor antagonists (AIIRAs), Losartan,.Vasartan

Renin is an enzyme produced by the kidney converts a circulating glycoprotein (angiotensinogen) into the biologically inert angiotensin I, which is then changed by angiotensin converting enzyme (ACE) into the highly potent vasoconstrictor angiotensin II. ACE is located on the luminal surface of capillary endothelial cells, Angiotensin II acts on two receptors, angiotensin 'AT1 ,AT2 lead to stimulationof aldosterone (the sodium-retaining hormone) production by the adrenal cortex. The antihypertensive effect of ACE inhibitors and AT1 receptor blockers results primarily from vasodilatation, A fall in aldosterone production may also contribute to the blood pressure lowering action of ACE inhibitors.



6-**Adrenergic neuron blocking** Guanethidine obsolete in HT

7-**Depletion of stored transmittirs** Reserpine obsolete in HT

8-**Autonomic ganglion blocking drugs** Hexamethonium Trimetaphan

9-**α2-ADRENOCEPTOR AGONISTS** Clonidine

10-**FALSE TRANSMITTER** Methyldopa.

PHARMACOLOGY OF THE ANTICOAGULANT DRUGS

The ideal anticoagulant drug would prevent pathologic thrombosis and limit reperfusion injury, yet allow a normal response to vascular injury and limit bleeding.

HEPARIN

Heparin binds to endothelial cell surfaces and a variety of plasma proteins. Its biologic activity is dependent upon the endogenous anticoagulant **antithrombin**. Antithrombin inhibits clotting factor proteases, especially thrombin (IIa), IXa, and Xa, by forming equimolar stable complexes with them.

LMW heparins such as **enoxaparin, dalteparin**, and **tinzaparin** are effective in several thromboembolic conditions.

Toxicity

A. Bleeding The major adverse effect of heparin is bleeding.

B. Heparin-Induced Thrombocytopenia

Contraindications

Heparin is contraindicated in patients with hypersensitivity to the drug, active bleeding, hemophilia, thrombocytopenia, purpura, severe hypertension, intracranial hemorrhage, infective endocarditis, ulcerative lesions in GIT, threatened abortion, visceral carcinoma, or advanced hepatic or renal disease.

patients who have recently had surgery of the brain, spinal cord, or eye, and in patients who are undergoing lumbar puncture or regional anesthetic block.

Despite the apparent, heparin should be used in pregnant women only when clearly indicated.

Reversal of Heparin Action

Excessive anticoagulant action of heparin is treated by discontinuance of the drug. If bleeding occurs, administration of a specific antagonist such as **Protamine sulfate** is indicated.

WARFARIN & THE COUMARIN ANTICOAGULANTS.

Warfarin is generally administered as the sodium salt and has 100% bioavailability.

Mechanism of Action

block the g-carboxylation of several glutamate residues in prothrombin and factors VII, IX, and X as well as the endogenous anticoagulant proteins C and S The blockade

Toxicity

Warfarin crosses the placenta readily and can cause a hemorrhagic disorder in the fetus. Furthermore, fetal proteins with g-carboxyglutamate residues found in bone and blood may be affected by warfarin;

the drug can cause a serious birth defect characterized by abnormal bone formation. Thus, warfarin should never be administered during pregnancy.

Cutaneous necrosis with reduced activity of protein C sometimes occurs during the first weeks of therapy.

Drug Interactions

oral anticoagulants often interact with other drugs and with disease states. These interactions can be divided into (Pharmacokinetic Interaction are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding.

Pharmacodynamic interactions with warfarin are synergism (impaired hemostasis, reduced clotting factor synthesis, as in hepatic disease), competitive antagonism (vitamin K), and an altered physiologic control loop for vitamin K (hereditary resistance to oral anticoagulants).

Reversal of Warfarin Action

Excessive anticoagulant effect and bleeding from warfarin can be reversed by stopping the drug and administering oral or parenteral vitamin K_1 (phytonadione

BASIC PHARMACOLOGY OF THE FIBRINOLYTIC DRUGS

Fibrinolytic drugs rapidly lyse thrombi by catalyzing the formation of the serine protease **plasmin** from its precursor. These drugs create a generalized lytic state when administered intravenously. Thrombolytic Drugs for Acute Myocardial Infarction in one major application.

Streptokinase is a protein (but not an enzyme in itself) synthesized by streptococci that combines with the proactivator plasminogen. This enzymatic complex catalyzes the conversion of inactive plasminogen to active plasmin. **Urokinase** is a human enzyme synthesized by the kidney that directly converts plasminogen to active plasmin. Plasmin itself cannot be used because naturally occurring inhibitors in plasma prevent its effects. However, the absence of inhibitors for urokinase and the streptokinase-proactivator complex permit their use clinically.

Anistreplase (anisoylated plasminogen streptokinase activator complex; APSAC) consists of a complex of purified human plasminogen and bacterial streptokinase that has been acylated to protect the enzyme's active site.

Thrombolytic Drugs For Acute Myocardial Infarction

Administration of fibrinolytic drugs by the intravenous route is indicated in cases of **pulmonary embolism with hemodynamic instability**, severe **deep venous thrombosis** such as the superior vena caval syndrome, **ascending thrombophlebitis** of the iliofemoral vein with severe lower extremity edema. These drugs are also given intra-arterially, especially for peripheral vascular disease.

BASIC PHARMACOLOGY OF ANTIPLATELET AGENTS

Platelet function is regulated by three categories of substances.

1- outside the platelet that interact with platelet membrane receptors, eg, catecholamines, collagen, thrombin, prostacyclin.

2- agents that interact with membrane receptors, eg, ADP, prostaglandin D_2, prostaglandin E_2, and serotonin.

3- agents act within the platelet(prostaglandin endoperoxides and thromboxane A_2 cAMP and cGMP, calcium ion.

ASPIRIN

The prostaglandin **thromboxane A_2** is an arachidonate product that causes platelets to change shape, release their granules, and aggregate , aspirin inhibits the synthesis of thromboxane A_2 by irreversible acetylation of the enzyme cyclooxygenase. Other salicylates and nonsteroidal anti-inflammatory drugs also inhibit cyclooxygenase but have a shorter duration of inhibitory action because they cannot acetylate cyclooxygenase; that is, their action is reversible.

CLOPIDOGREL & TICLOPIDINE

Clopidogrel and ticlopidine reduce platelet aggregation by inhibiting the ADP pathway of platelets. These drugs that achieve their antiplatelet effects by irreversibly blocking the ADP receptor on platelets. Unlike aspirin, these drugs have no effect on prostaglandin metabolism.

Adverse effects of ticlopidine include nausea, dyspepsia, and diarrhea in up to 20% of patients, hemorrhage in 5%, and, leukopenia in 1%. The dosage of ticlopidine is 250 mg twice daily. It is particularly useful in patients who cannot tolerate aspirin. Doses of ticlopidine less than 500 mg/d may be efficacious with fewer adverse effects.

Clopidogrel has fewer adverse effects than ticlopidine and is rarely associated with neutropenia. Thrombotic thrombocytopenic purpura associated with clopidogrel has been reported. Because of its superior side effect profile and dosing requirements, clopidogrel is preferred over ticlopidine.

ADDITIONAL ANTIPLATELET-DIRECTED DRUGS

Dipyridamole is a vasodilator that inhibits platelet function by inhibiting adenosine uptake and cyclic GMP phosphodiesterase activity. Dipyridamole by itself has little or no beneficial effect. Therapeutic use is primarily in combination with aspirin to prevent cerebrovascular ischemia. also used in combination with warfarin for primary prophylaxis of thromboemboli in patients with prosthetic heart valves..

Cilostazol is a newer phosphodiesterase inhibitor that promotes vasodilation and inhibition of platelet aggregation. Cilostazol is used primarily to treat intermittent claudication.

DRUGS USED IN BLEEDING DISORDERS

VITAMIN K

Vitamin K confers biologic activity upon prothrombin and factors VII, IX, and X by participating in their postribosomal modification..

Vitamin K_1 is available clinically in oral and parenteral forms. Onset of effect is delayed for 6 hours but the effect is complete by 24 hours when treating depression of prothrombin activity by excess warfarin or vitamin K deficiency. Intravenous administration of vitamin K_1 should be slow, because rapid infusion can produce dyspnea, chest and back pain, and even death

Vitamin K_1 is currently administered to all newborns to prevent the hemorrhagic disease of vitamin K deficiency,

PLASMA FRACTIONS

Deficiencies in plasma coagulation factors can cause bleeding. Spontaneous bleeding occurs when factor activity is less than 5-10% of normal. Factor VIII deficiency **(classic hemophilia**, or **hemophilia A)** and factor IX deficiency **(Christmas disease**, or **hemophilia B)**

Clinical Uses

An uncomplicated hemorrhage into a joint should be treated with sufficient factor VIII or factor IX replacement to maintain a level of at least 30-50% of the normal concentration for 24 hours.

Desmopressin acetate increases the factor VIII activity of patients with mild hemophilia A or von Willebrand disease. It can be used in preparation for minor surgery such as tooth extraction without any requirement for infusion of clotting

Cryoprecipitate is a plasma protein fraction obtainable from whole blood. It is used to treat deficiencies or qualitative abnormalities of fibrinogen, disseminated intravascular coagulation and liver disease. A single unit of cryoprecipitate contains 300 mg of fibrinogen.Cryoprecipitate may also be used in factor VIII deficiency and von Willebrand disease

FIBRINOLYTIC INHIBITORS: AMINOCAPROIC ACID

Aminocaproic acid (EACA), which is chemically similar to the amino acid lysine, is a synthetic inhibitor of fibrinolysis. It competitively inhibits plasminogen.

Tranexamic acid

is an analog of aminocaproic acid and has the same properties. Clinical uses of aminocaproic acid are as adjunctive therapy in hemophilia, as therapy for bleeding from fibrinolytic therapy, and as prophylaxis for rebleeding from intracranial aneurysms.

SERINE PROTEASE INHIBITORS: APROTININ

serine protease inhibitor ("serpin") that inhibits fibrinolysis by free plasmin and may have other antihemorrhagic effects as well. It also inhibits the plasmin-streptokinase complex in patients who have received that thrombolytic agent.

Histamine, Serotonin, , the Ergot Alkaloids

. CLINICAL PHARMACOLOGY OF HISTAMINE

In pulmonary function laboratories, histamine aerosol has been used as a provocative test of **bronchial hyperreactivity**.. Histamine should not be given to patients with asthma (except as part of a carefully monitored test of pulmonary function) or to patients with active ulcer disease or gastrointestinal bleeding. **Beta hestine** is histamine analoge used in meniere-s disease

Histamine Antagonists

H_1- H_2-H_3- H_4-Receptor Antagonists

(**Azelastine Cetirizine Chlorpheniramine Clemastine Cyclizine Cyproheptadine Desloratadine Dexchlorpheniramine Dimenhydrinate Diphenhydramine Fexofenadine Hydroxyzine Ketotifen Loratadine Meclizine Promethazine Triprolidine**)

SEROTONIN (5-HYDROXYTRYPTAMINE)

Serotonin is an important neurotransmitter, a local hormone in the gut, a component of the platelet clotting process, and is thought to play a role in migraine headache. serotonin is present in a variety of sites in the brain. Its role as a neurotransmitter and its relation to the actions of drugs acting in the central nervous system

5-HT_3 receptors in the gastrointestinal tract and in the vomiting center of the medulla participate in the vomiting reflex particularly important in vomiting caused by chemical such as cancer chemotherapy drugs. 5-HT_{1P} and 5-HT_4 receptors play a role in nervous system function.

MELATONIN PHARMACOLOGY

Melatonin is produced and released primarily at night and has long been suspected of playing a role in diurnal cycles of animals and the sleep-wake behavior of humans.

Melatonin receptors have been characterized in the central nervous system and several peripheral tissues.
In the brain, MT_1 and MT_2 receptors are found in membranes of the hypothalamus,
MT_3, is an enzyme; with a poorly defined physiologic role, possibly related to intraocular pressure.

Activation of the MT_1 receptor results in sleepiness, whereas the MT_2 receptor may be related to the light-dark synchronization of the biologic circadian clock.

Melatonin itself is promoted commercially as a sleep aid by the food supplement

Ramelteon is a selective MT_1 and MT_2 agonist that has recently been approved for the medical treatment of insomnia. This drug has no addiction liability (it is not a controlled substance), appears to be distinctly more efficacious than melatonin (but less efficacious than benzodiazepines) as a hypnotic.

Clinical Pharmacology Of Serotonin Agonists

5-$HT_{1D/1B}$ Agonists Migraine Headache

The 5-$HT_{1D/1B}$ agonists (**triptans**) are used in migraine headache. **Sumatriptan , almotriptan, sumatriptan, rizatriptan, zolmitriptan** because of the ability of drugs to cause coronary vasospasm. They contraindicated in patients with coronary artery disease and in angina.

Cisapride, used in the treatment of gastroesophageal reflux and motility disorders. Because of toxicity, it is now not used .

Tegaserod, partial agonist, used for irritable bowel with constipation.
Fluoxetine and other SSRIs, blocking reuptake of the transmitter, used for the management of depression and similar disorders.

SEROTONIN-RECEPTOR ANTAGONISTS

Cyproheptadine potent H_1-receptor-blocking , 5-HT_2-blocking actions. has significant antimuscarinic effects .The major clinical applications of cyproheptadine are urticaria..

Ketanserin blocks 5-HT_2 receptors on platelets and antagonizes platelet aggregation promoted by serotonin. blocks α_1 adrenoceptors. **(Ritanserin**, 5-HT_2 antagonist, has little or no α blocking action).

Ondansetron is the prototypical 5-HT_3 antagonist. This drug and its analogs are very important in the prevention of nausea and vomiting associated with surgery and cancer chemotherapy.

ERGOT ALKALOIDS

Clinical Uses

MIGRAINE Ergot derivatives are highly specific for migraine pain; **ergotamine** effective when given during the prodrome of an attack; Ergotamine available for oral, sublingual, rectal supp., and inhaler use. . **Dihydroergotamine**, 0.5-1 mg intravenously, for treatment of intractable migraine. Intranasal dihydroergotamine also be effective.

B. HYPERPROLACTINEMIA

Treatment of hyperprolactinemia is **Bromocriptine Cabergoline**

C. POSTPARTUM HEMORRHAGE

Ergonovine maleate, 0.2 mg usually given intramuscularly, can be effective within 1-5 minutes and less toxic than other ergot derivatives

D. DIAGNOSIS OF VARIANT ANGINA

Ergonovine given intravenously produces prompt vasoconstriction during coronary angiography to diagnose variant angina

Toxicity -Contraindications

The common toxic effects of ergot derivatives are GI disturbances, including diarrhea, nausea, and vomiting. A more dangerous toxic effect of overdosage is prolonged vasospasm. Peripheral vascular vasospasm infusions of large doses of nitroprusside or GTN have successful in some cases.

DRUGS AND GOUT

Gout is a metabolic disease characterized by recurrent episodes of acute arthritis due to deposits of monosodium urate in joints and cartilage. Uric acid renal calculi, tophi, and interstitial nephritis may also occur. Gout is usually associated with high serum levels of uric acid, a poorly soluble substance that is the major end product of purine metabolism. The treatment of gout aims to relieve acute gouty attacks and to prevent recurrent gouty episodes and urate lithiasis.

Drugs used for prophylaxis and treatment of gout:

Colchicine

Colchicine relieves the pain and inflammation of gouty arthritis in 12-24 hours without altering the metabolism or excretion of urates and without other analgesic effects.. Colchicine is now used for the prophylaxis of recurrent episodes of gouty arthritis

Colchicine often causes diarrhea and may occasionally cause nausea, vomiting, and abdominal pain. Colchicine may rarely cause hair loss and bone marrow depression , peripheral neuritis ,myopathy.

NSAIDS IN GOUT

In addition to inhibiting prostaglandin synthase, indomethacin and other NSAIDs also inhibit urate crystal phagocytosis. Indomethacin is commonly used as initial treatment of gout as the replacement for colchicine.

All other NSAIDs except aspirin, salicylates, and tolmetin have been successfully used to treat acute gouty episodes.

URICOSURIC AGENTS

Probenecid and sulfinpyrazone are uricosuric drugs employed to decrease the body pool of urate in patients with tophaceous gout.. Uricosuric therapy should be initiated in gouty underexcretion of uric acid when allopurinol or febuxostat is contraindicated or when evidence of tophi appears. Therapy should not be started until 2-3 weeks after an acute attack.

Nephrotic syndrome has occurred after the use of probenecid. Both sulfinpyrazone and probenecid may rarely cause aplastic anemia.

ALLOPURINOL

The preferred therapy for gout is allopurinol, which reduces total uric acid body burden by inhibiting xanthine oxidase resulting in a fall in the plasma urate level and a decrease in the size of the urate pool. Treatment of gout with allopurinol, as with uricosuric agents, is begun with the expectation that it will be continued for years if not for life.

Adverse Effects

nausea, vomiting, and diarrhea, may occur. Peripheral neuritis and necrotizing vasculitis, depression of bone marrow elements, and, rarely, aplastic anemia may also occur. Hepatic toxicity and interstitial nephritis have been reported..

FEBUXOSTAT

Febuxostat is a potent and selective nonpurine inhibitor of xanthine oxidase, and thereby reduces the formation of xanthine and uric acid..

Vitamins

Vitamins are required for normal body metabolism, growth, development. They are components of enzyme systems that release energy from proteins, fats, and carbohydrates. They also required for formation of red blood cells, nerve cells, hormones, genetic materials, bones, and other tissues. They are effective in small amounts and are mainly obtained from foods or supplements.

Vitamins are usually classified as
fat soluble (A, D, E, K) and water soluble (B complex, C).

Fat-soluble vitamins are absorbed
from the intestine with dietary fat, and absorption requires the presence of bile salts and pancreatic lipase. These vitamins are relatively stable in cooking.

Water-soluble vitamins are readily absorbed but are also readily lost by cooking and storage.

Vitamin disorders should be recognized as early as possible
and appropriate treatment initiated. Early recognition treatment can prevent a mild deficiency or excess from becoming severe.

General guidelines of vitamin therapy include the following

1-For deficiency states, oral vitamin preparations are preferred when possible. They are usually effective (exception alabsorption syndromes), safe, convenient to administer, and relatively inexpensive. Multiple deficiencies are common, and multivitamin preparation used usually contains more than the recommended daily amount.

2- For excess states, the usual treatment is to stop administration of the vitamin preparation.

Disorders of Fat-Soluble Vitamin A

• With vitamin A deficiency, increase intake of foods containing vitamin A or beta carotene. Use a single, pure form of vitamin A rather than a multivitamin, unless multiple deficiencies are present. Give doses no larger than 25,000 U daily unless a severe deficiency is present. Give orally if not contraindicated; give intramuscularly if gastrointestinal (GI) absorption is severely impaired or ocular symptoms are severe. With vitamin A excess, immediately stop known sources of the vitamin.

Disorders of Fat-Soluble Vitamin K

• With vitamin K deficiency, bleeding may occur spontaneously or in response to trauma. Thus, administration of vitamin K and measures to prevent bleeding are indicated. If the deficiency is not severe, oral vitamin K may be given for a few days until serum prothrombin activity returns to a normal range.. In severe bleeding may be given intravenously

Disorders of B-Complex Vitamins

Most deficiencies of B-complex vitamins are multiple rather than single If a single deficiency seems predominant, that vitamin may be given alone or along with a multivitamin preparation. Thiamine deficiency is common in alcoholics. Reasons include inadequate dietary intake , One type occurs with pyridoxine deficiency and is relieved by administration of pyridoxine.

Megaloblastic anemia's, characterized by abnormally large, immature red blood cells, occur with deficiency of folic acid or vitamin B12. If megaloblastic anemia is severe, treatment is usually instituted with both folic acid and vitamin B12. In pernicious anemia, vitamin B12 must be given by injection because oral forms are not absorbed from the GI tract.

Disorders of Vitamin C

Treatment of vitamin C deficiency involves increased intake of vitamin C from dietary or pharmaceutical sources. Vitamin C is available alone for oral, intramuscular (IM), or IV administration. It is also an ingredient in most multivitamin preparations for oral or parenteral use

Use of vitamins in Older Adults

Vitamin requirements are the same as for younger adults. However, deficiencies are common in older adults, especially of vitamins A and D, cyanocobalamin (B12), folic acid, riboflavin,
and thiamine. With vitamin B12, for example, it is estimated that older adults absorb only 10% to 30% of the amount found in food.

Minerals and Electrolytes

Minerals and electrolytes are essential constituents of bone, teeth, cell membranes, connective tissue, and many essential enzymes. They function to maintain fluid, electrolyte, and acid–base balance; maintain osmotic pressure; maintain nerve and muscle function; assist in transfer of compounds across cell membranes; and influence the growth process.

Macronutrients

Some minerals (calcium, phosphorus, sodium, potassium, magnesium, chlorine, sulfur) are required in relatively large amounts (>100 mg) and thus are sometimes called *macronutrients*

Micronutrients or trace elements. trace elements (chromium, cobalt, copper, fluoride, iodine ,iron, selenium, and zinc*)*

Principles Of Therapy

When a mineral is given to correct a deficiency state, there is a risk of producing an excess state. Because both deficiency and excess states may be harmful, the amount of mineral supplement should be titrated closely to the amount needed by the body.

Drug Selection

Oral drug preparations are preferred, when feasible, for preventing or treating mineral disorders. They are safer, less likely to produce toxicity, more convenient to administer, and less expensive than parenteral preparation

Pancreatic Hormones

Antidiabetic Drugs

The endocrine of pancreas in the adult human consists of approximately 1 million islets of Langerhans. Their hormone products include **insulin**, the storage and anabolic hormone of the body; The elevated blood glucose associated with diabetes mellitus results from absent or inadequate pancreatic insulin secretion, with or without concurrent impairment of insulin action. The disease states underlying the diagnosis of diabetes mellitus are now classified into categories:

Type 1, Insulin-dependent diabetes mellitus.
Type 2, Non insulin-dependent diabetes mellitus.
Type 3, other
Type 4 , Gestational diabetes mellitus.

Insulin is released from pancreatic B cells at a low basal rate and at a much higher stimulated rate in response to a variety of stimuli, especially glucose. The liver and kidney are the two main organs that remove insulin from the circulation.

Insulin promotes the storage of fat as well as glucose (both sources of energy) within specialized target cells) and influences cell growth and the metabolic functions of a wide variety of tissues.

Principal Types And Duration Of Action Of Insulin Preparations:

A-Short Acting
1-Regular short acting soluble crystalline zinc
2-Rapidly acting Insulin analogs(lispro-Humo-log)

B-Long acting Insulin
1- NPH Neutral protamine Hagedorn or Isophane Insulin
2- Insulin glargine
3- Insulin detemir
4- Insulin Degludec
5- Mixture of insulins

Complications of Insulin Therapy:

A. Hypoglycemia

The most common complication of insulin therapy. They may result from a delay in taking a meal, inadequate carbohydrate consumed, unusual physical exertion, or a dose of insulin that is too large . All the manifestations of hypoglycemia are relieved by glucose administration

B. Immunopathology Of Insulin Therapy

1. Insulin Allergy

2. Immune Insulin Resistance

C. Lipodystrophy At Injection Sites

Oral Antidiabetic Agents

1-**Insulin Secretagogues: Sulfonylureas-**

The major action of sulfonylurea is to increase insulin release from the pancreas . Two additional mechanisms of action have been proposed reduction of serum glucagon levels and closure of potassium channels in extra pancreatic tissues. **Glibenaclamide Glimepiride**

2-BIGUANIDES

Mechanisms of action include

(1) Reduced hepatic and renal gluconeogenesis.

(2) Slowing of glucose absorption from the gastrointestinal tract, with increased glucose to lactate conversion by enterocytes.

(3) Direct stimulation of glycolysis in tissues, with increased glucose removal from blood.

(4) Reduction of plasma glucagon levels.

Metformin is useful in the prevention of type 2 diabetes

500 mg to a maximum of 2.550 g daily, The most common toxic effects of metformin are gastrointestinal (anorexia, nausea, vomiting, abdominal discomfort, diarrhea) and occur in up to 20% of patients. Biguanides are contraindicated in patients with renal disease, alcoholism, hepatic disease

THIAZOLIDINEDIONES

Thiazolidinediones (Tzds) act to decrease insulin resistance. Their primary action is the regulation of genes involved in glucose and lipid metabolism **Pioglitazone** **Rosiglitazone**

ALPHA-GLUCOSIDASE INHIBITORS

Acarbose and **miglitol** are competitive inhibitors of the intestinal a-glucosidases and reduce the postprandial digestion and absorption of starch and disaccharides.

. Adrenocorticosteroids - Adrenocortical Antagonists

The natural adrenocortical hormones are steroid molecules produced and released by the adrenal cortex. Both natural and synthetic corticosteroids are used for diagnosis and treatment of disorders of adrenal function. They are also used more often and in much larger doses for treatment of a variety of inflammatory and immunologic disorders.

Secretion of adrenocortical steroids is controlled by the pituitary release of corticotropin (ACTH). Secretion of the salt-retaining hormone aldosterone is primarily under the influence of angiotensin. Corticotropin has some actions that do not depend upon its effect on adrenocortical secretion.

Inhibitors of the synthesis or antagonists of the action of the adrenocortical steroids are important in the treatment of several conditions.

SYNTHETIC CORTICOSTEROIDS

Glucocorticoids have become important agents for use in the treatment of many inflammatory, immunologic, hematologic, and other disorders. This has stimulated development of synthetic steroids with anti-inflammatory ,immunosuppressive activity. The actions of the synthetic steroids are similar to those of cortisol They bind to the specific intracellular receptor proteins and produce the same effects but have different ratios of glucocorticoid to mineralocorticoid potency

Clinical Pharmacology

1-. Diagnosis And Treatment Of Disturbed Adrenal Function

2- Corticosteroids Stimulation Of Lung Maturation In The Fetus

Lung maturation in the fetus is regulated by the fetal secretion of cortisol. Treatment of the mother with large doses of glucocorticoid reduces the incidence of respiratory distress syndrome in infants delivered prematurely. When delivery is anticipated before 34 weeks of gestation, intramuscular betamethasone, 12 mg, followed by an additional dose of 12 mg 18-24 hours later, is commonly used

3. CORTICOSTEROIDS AND NONADRENAL DISORDERS

Disorder	Examples
Allergic reactions	Angioneurotic edema, asthma, bee stings, contact dermatitis, drug reactions, allergic rhinitis, serum sickness, urticaria
Collagen-vascular disorders	Giant cell arteritis, lupus erythematosus, mixed connective tissue syndromes, polymyositis, polymyalgia rheumatica, rheumatoid arthritis, temporal arteritis
Eye diseases	Acute uveitis, allergic conjunctivitis, choroiditis, optic neuritis
Gastrointestinal diseases	Inflammatory bowel disease, nontropical sprue, subacute hepatic necrosis
Hematologic disorders	Acquired hemolytic anemia, acute allergic purpura, leukemia, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, multiple myeloma
Systemic inflammation	Acute respiratory distress syndrome (sustained therapy with moderate dosage accelerates recovery and decreases mortality)
Infections	Acute respiratory distress syndrome, sepsis, systemic inflammatory syndrome
Inflammatory conditions of bones and joints	Arthritis, bursitis, tenosynovitis
Neurologic disorders	Cerebral edema (large doses of dexamethasone are given to patients following brain surgery to minimize cerebral edema in the postoperative period), multiple sclerosis
Organ transplants	Prevention and treatment of rejection (immunosuppression)
Pulmonary diseases	Aspiration pneumonia, bronchial asthma, prevention of infant respiratory distress syndrome, sarcoidosis
Renal disorders	Nephrotic syndrome
Skin diseases	Atopic dermatitis, dermatoses, lichen simplex chronicus (localized neurodermatitis), mycosis fungoides, pemphigus, seborrheic dermatitis, xerosis
Thyroid diseases	Malignant exophthalmos, subacute thyroiditis
Miscellaneous	Hypercalcemia, mountain sickness

SIDE EFFECT :

When the glucocorticoids are used for short periods 2 weeks), is unusual to see serious adverse effects even with moderately large doses. However, insomnia, behavioral changes and acute peptic ulcers are occasionally observed even after only a few days of treatment. Acute pancreatitis is a rare but serious acute adverse effect of high-dose glucocorticoids.

Most patients who are given daily doses of 100 mg of hydrocortisone or more (or the equivalent amount of synthetic steroid) for longer than 2 weeks undergo a series iatrogenic Cushing's syndrome.

. In the face, rounding, puffiness, fat deposition, and plethora usually appear (moon facies). . There is an increased growth of fine hair over the face, and increased appetite are noted

. . Other serious side effects peptic ulcers and their consequences. increased intraocular pressure is common, and glaucoma may be induced.

SPECIAL PRECAUTIONS

Patients receiving these drugs must be monitored carefully for the development of hyperglycemia, glycosuria, sodium retention with edema or hypertension, hypokalemia, peptic ulcer, osteoporosis, and hidden infections.

CONTRAINDICATIONS

These agents must be used with great caution in patients with peptic ulcer, heart disease or hypertension with heart failure, certain infectious illnesses such as varicella and tuberculosis, psychoses, diabetes, osteoporosis, or glaucoma.

PREPARATIONS AVAILABLE[1]

Glucocorticoids For Oral Parenteral Use

Betamethasone Cortisone Dexamethasone

Dexamethasone sodium phosphate Hydrocortisone acetate

Methylprednisolone Methylprednisolone acetate

Methylprednisolone sodium succinate (Prednisolone

Triamcinolone Triamcinolone acetonide

MINERALOCORTICOIDS (ALDOSTERONE, DEOXYCORTICOSTERONE, FLUDROCORTISONE)

1. Aldosterone Aldosterone and other steroids with mineralocorticoid properties promote the reabsorption of sodium from the distal part of the distal convoluted tubule and from the cortical collecting renal tubules, mineralocorticoids lead to hypokalemia, metabolic alkalosis, increased plasma volume, and hypertension.

2. Deoxycorticosterone (DOC) serves as a precursor of aldosterone

3. Fludrocortisone potent steroid with both glucocorticoid and mineralocorticoid activity, is the most widely used mineralocorticoid.

ADRENAL ANDROGENS

The adrenal cortex secretes large amounts of DHEA and smaller amounts of androstenedione and testosterone. Although these androgens are thought to contribute to the normal maturation process,.

ANTAGONISTS OF ADRENOCORTICAL AGENTS

Synthesis Inhibitors Glucocorticoid Antagonists

1. Metyrapone 2. Aminoglutethimide 3. Ketoconazole

Mineralocorticoid Antagonists

Spironolactone Eplerenone, Drospirenone.

Thyroid and Antithyroid Drugs

The normal thyroid gland secretes sufficient amounts of thyroid hormones triiodothyronine (T_3) and tetraiodothyronine (T_4, thyroxine). The thyroid hormones responsible for optimal growth, development, function, and maintenance of all body tissues. Excess or inadequate amounts result in the signs and symptoms of hyperthyroidism or hypothyroidism, respectively).

Synthetic levothyroxine is the preparation of choice for thyroid replacement and suppression therapy because of its: **Stability. Content Uniformity Low Cost. Lack Of Allergenic Foreign Protein**,.

ANTITHYROID AGENTS:

Reduction of thyroid activity and hormone effects can be accomplished by agents that: **interfere with the production of thyroid hormones, by agents that modify the tissue response to thyroid hormones, or by glandular destruction with radiation or surgery..**

1. Thioamides

carbimazole methimazole and **propylthiouracil** are major thioamides drugs for treatment of thyrotoxicosis., ,..

2. Iodides: Prior to introduction of the thioamides in the 1940s, iodides were the major antithyroid agents; they are rarely used.

3. Beta Adrenoceptor-Blocking Agents

Beta blockers (eg, metoprolol, propranolol, atenolol) are effective therapeutic adjuncts in the management of thyrotoxicosis. Propranolol has been the most widely used in the therapy of thyrotoxicosis. Beta blockers cause clinical improvement of hyperthyroid symptoms but do not alter thyroid hormone levels.

Anterior Pituitary Hormones Hypothalamic Regulators

All of the hormones produced by the anterior pituitary except prolactin (PRL) are key participants in hormonal systems in which they regulate the production by peripheral tissues of hormones that perform the ultimate regulatory functions. In these systems, the secretion of the pituitary hormone is under the control of a hypothalamic hormone. Each hypothalamic-pituitary-endocrine gland system or axis provides multiple complex neuroendocrine regulation of growth, development, and reproductive functions.

GROWTH HORMONE (SOMATOTROPIN)

Growth hormone, one of the peptide hormones produced by the anterior pituitary, is required during childhood and adolescence for attainment of normal adult size and has important effects throughout life, Growth hormone **(somatotropin)** Two types of recombinant human growth hormone. **Somatropin**. **Somatrem**

GROWTH HORMONE DEFICIENCY

Growth hormone deficiency can have a genetic basis or can be acquired as a result of damage to the pituitary or hypothalamus by tumor, infection, surgery, or radiation therapy. In childhood, GH deficiency presents as short stature. Treatment of children with short stature by GH. Treatment is begun with 0.025 mg/kg daily and may be increased to a maximum of 0.045 mg/kg daily.

Other Uses of Growth Hormone

Growth hormone affects many organ systems and also has a net anabolic effect. It has been tested in a number of conditions that are associated with a severe catabolic state and is approved for the treatment of wasting in patients with AIDS. Growth hormone is a popular component of anti-aging programs.

GROWTH HORMONE ANTAGONISTS

In adults, **Acromegaly**, which is characterized by abnormal growth of cartilage and bone tissue, and many organs including skin, muscle, heart, liver, and the gastrointestinal tract. Acromegaly adversely affects the skeletal, muscular, cardiovascular, respiratory, and metabolic systems. When a GH-secreting adenoma occurs before the long bone epiphyses close, it leads to the rare condition, **Gigantism**. **Acromegaly,, Gigantism**. can be treated with GH antagonists. **Octreotide**, a somatostatin analog, and **Bromocriptine**.

The Gonadotropins

(Follicle-Stimulating Hormone FSH

&Luteinizing Hormone& Human Chorionic Gonadotropin)

These hormones serve complementary functions in the reproductive process. In women, the principal function of FSH is to direct ovarian follicle development., LH stimulates androgen production. In the luteal phase of the menstrual cycle.

Estrogen and Progesterone production is primarily under the control first of LH and then, if pregnancy occurs, under the control of human chorionic gonadotropin (HCG)of placenta.

In men, FSH is the primary regulator of spermatogenesis, whereas LH is the main stimulus for the production of testosterone by Leydig cells. FSH helps to maintain high local androgen concentrations in the developing sperm.

Clinical Pharmacology of Gonadotropin

A. Ovulation Induction

The gonadotropins are used to induce ovulation in women with anovulation due to hypogonadism **Clomiphene "clomid"**

B. Male Infertility

Most of the signs and symptoms of hypogonadism in males (eg, delayed puberty, maintenance of secondary sex characteristics after puberty) can be adequately treated with exogenous androgen therapy has consisted of initial treatment for 8-12 weeks with injections of 1000-2500 IU HCG several times per week.

C . Female infertility

Gonadotropin can be used to precipitate an LH surge and ovulation in women with infertility who are undergoing ovulation induction

SUPPRESSION OF GONADOTROPIN PRODUCTION

1. Controlled ovarian hyperstimulation

2. Endometriosis is cyclical abdominal pain in premenopausal women due to the presence of endometrium-like tissue outside the uterus.

3 Prostate cancer Antiandrogen therapy is the primary medical therapy for prostate cancer. such as **Flutamide..**

4. Central precocious puberty (onset of secondary sex characteristics before 8 years in girls or 9 years in boys). Continuous administration of a GnRIH agonist is indicated.

PROLACTIN

. Prolactin is the principal hormone responsible for lactation. Milk production is stimulated by prolactin. A deficiency of prolactin which can manifested by failure to lactate,. Prolactin levels may be elevated as a result of impaired transport of dopamine (prolactin-inhibiting hormone) to the pituitary. Hyperprolactinemia produces a syndrome of amenorrhea and galactorrhea in women, and loss of libido and infertility in men. No preparation of prolactin is available for use in prolactin-deficient patients. For patients with symptomatic hyperprolactinemia, inhibition of prolactin secretion can be achieved with dopamine agonists, which act in the pituitary to inhibit prolactin release.

Bromocriptine,

cabergoline,

Used in

1- Hyperprolactinemia

2- Suppress lactation when breast feeding was not desired

3- Acromegaly.

POSTERIOR PITUITARY HORMONES

The two posterior pituitary hormones vasopressin and oxytocin are synthesized in neuronal cell bodies in the hypothalamus and then transported via their axons to the posterior pituitary, where they are stored and then released into the circulation.

OXYTOCIN

Oxytocin is a peptide hormone secreted by the posterior pituitary that participates in labor and delivery and elicits milk ejection in lactating women.. usually administered intravenously via an infusion

VASOPRESSIN (ANTIDIURETIC HORMONE, ADH)

Vasopressin is a peptide hormone released by the posterior pituitary in response to rising plasma tonicity or falling blood pressure.
Vasopressin possesses antidiuretic and vasopressor properties.
A deficiency of this hormone results in diabetes insipidus

Desmopressin acetate is a long-acting synthetic analog of vasopressin can be administered intravenously, subcutaneously, intranasally, or orally. Vasopressin and desmopressin are treatments of choice for pituitary diabetes insipidus.

The Ovary (Estrogens, Progestins, Ovarian Hormones, Inhibitors & Antagonists, & Ovulation-Inducing Agents ,Oral Contraceptives,)

The ovary has important functions that are integrated with its hormonal activity. In the human female, the gonad is relatively quiescent during childhood, the period of rapid growth and maturation. At puberty, the ovary begins a 30- to 35-year period of cyclic function called the **menstrual cycle** because of the regular episodes of bleeding that are its most obvious manifestation. It then fails to respond to gonadotropins secreted by the anterior pituitary gland, and the cessation of cyclic bleeding that occurs is called the **menopause.**

At the beginning of each cycle, a variable number of follicles (vesicular follicles), each containing an ovum, begin to enlarge in response to FSH. After 5 or 6 days, one follicle, called the dominant follicle, begins to develop more rapidly. The outer theca and inner granulosa cells of this follicle multiply and, under the influence of LH, synthesize and release estrogens at an increasing rate. The estrogens appear to inhibit FSH release and may lead to regression of the smaller, less mature follicles. The mature dominant ovarian follicle consists of an ovum surrounded by a fluid-filled antrum lined by granulosa and theca cells.

The estrogen secretion reaches a peak just before midcycle, and the granulosa cells begin to secrete progesterone. These changes stimulate the brief surge in LH and FSH release that precedes and causes ovulation. When the follicle ruptures, the ovum is released into the abdominal cavity near the opening of the uterine tube,.Following the above events, the cavity of the ruptured follicle fills with blood and the luteinized theca and granulosa cells proliferate and replace the blood to form the corpus luteum. The cells of this structure produce estrogens and progesterone for the remainder of the cycle, or longer if pregnancy occurs.

If pregnancy does not occur, the corpus luteum begins to degenerate and ceases hormone production, eventually becoming a corpus albicans. The endometrium,

which proliferated during the follicular phase and developed its glandular function during the luteal phase, process of menstruation occur .

ESTROGENS

FEMALE MATURATION

Estrogens are required for the normal sexual maturation and growth of the female. They stimulate the development of the vagina, uterus, and uterine tubes as well as the secondary sex characteristics. They stimulate stromal development and ductal growth in the breast and are responsible for the accelerated growth phase and the closing of the epiphyses of the long bones that occur at puberty. They contribute to the growth of axillary and pubic hair and alter the distribution of body fat to produce typical female body contours. Larger quantities also stimulate development of pigmentation in the skin, most prominent in the region of the nipples and areolae and in the genital region

.

Clinical Uses

Estrogens have been used extensively for replacement therapy in estrogen-deficient patients. Post menopausal hormonal therapy

Adverse Effects

Nausea and breast tenderness are common and can be minimized by using the smallest effective dose of estrogen. Hyperpigmentation also occurs. Estrogen therapy is associated with an increase in frequency of migraine headaches as well as cholestasis, gallbladder disease, and hypertension ,**Uterine bleeding . Cancer**

THE PROGESTINS

Progesterone is the most important progestin in humans. It is synthesized in the ovary, from circulating cholesterol. Large amounts are also synthesized and released by the placenta during pregnancy

.

Therapeutic Applications

The major uses of progestin hormones are for hormone replacement therapy and hormonal contraception In addition, they are useful in producing long-term ovarian suppression for other purposes..

Medroxyprogesterone acetate, 10-20 mg orally twice weekly or intramuscularly in doses of 100 mg/m^2 every 1-2 weeks will prevent menstruation.

HORMONAL CONTRACEPTION

A large number of oral contraceptives containing estrogens or progestins (or both) are now available for clinical use.

Two types of preparations are used for oral contraception:

(1) combinations of estrogens and progestins and

(2) continuous progestin therapy without estrogens.

Several hormonal contraceptives are available as vaginal rings or intrauterine devices. Intramuscular injection of large doses of **Medroxyprogesterone** also provides contraception of long duration.

The combinations of estrogens and progestins exert their contraceptive effect largely through selective inhibition of pituitary function that results in inhibition of ovulation.

EFFECTS ON THE OVARY

Chronic use of combination agents depresses ovarian function. Follicular development is minimal,. The ovaries usually become smaller even when enlarged before therapy.

The great majority of patients return to normal menstrual patterns when these drugs are discontinued. About 75% will ovulate in the first post treatment cycle and 97% by the third post treatment cycle. About 2% of patients remain amenorrheic for periods of up to several years after administration is stopped.

EFFECTS ON THE BREAST

Stimulation of the breasts occurs in most patients receiving estrogen-containing agents administration of estrogens and combinations of estrogens ,progestins suppress lactation.(type for lactating mother)

OTHER EFFECTS OF ORAL CONTRACEPTIVES

1. Effects on the central nervous system

Estrogens tend to increase excitability in the brain, whereas progesterone tends to decrease it.

2. Effects on endocrine function ,The inhibition of pituitary gonadotropin secretion has been mentioned.

3. Effects on blood Serious thromboembolic phenomena occurring in women taking oral contraceptives

4. Effects on the liver These hormones also have profound effects on the function of the liver.

5. Effects on lipid metabolism

6. Effects on carbohydrate metabolism

7. Effects on the cardiovascular system These agents cause small increases in cardiac output associated with higher systolic and diastolic blood pressure and heart rate.

8. Effects on the skin The oral contraceptives have been increase pigmentation of the skin (chloasma). This effect seems to be enhanced in women with dark complexions and by exposure to ultraviolet light. Some of the androgen-like progestins might increase the production of sebum, causing acne in some patients.

Contraception with Progestins Alone

Small doses of progestins administered orally or by implantation under the skin can be used for contraception.

Effective contraception can also be achieved by injecting 150 mg of **Depot medroxyprogesterone acetate (DMPA)** every 3 months

Postcoital Contraceptives

Pregnancy can be prevented following coitus by the administration of estrogens alone or in combination with progestins (**"morning after coitus "** contraception). When treatment is begun within 72 hours,(2,2) it is effective 99% of the time..

Beneficial Effects of Oral Contraceptives

These include a reduced risk of ovarian cysts, ovarian and endometrial cancer, and benign breast disease. There is a lower incidence of ectopic pregnancy. Iron deficiency and rheumatoid arthritis are less common, and premenstrual symptoms, dysmenorrhea, endometriosis,

Clinical Uses

The most important use of combined estrogens and progestins is for oral contraception. Progestins and estrogens are also useful in the treatment of endometriosis. the suppression of ovulation

Adverse Effects of oral contraceptives

A. MILD ADVERSE EFFECTS

Nausea, Headache is mild and often transient. However, migraine is often made worse

B. MODERATE ADVERSE EFFECTS

May require discontinuance of oral contraceptives:

1. Bleeding in using progestin agents alone for contraception.

2. Weight gain is more common with the combination agents

3. Increased skin pigmentation may occur,

4. Hirsutism "combinations containing nonandrogenic progestins are preferred in these patients".

5. Ureteral dilation

7. Vaginal infections

8. Amenorrhea occurs in some patients

C. SEVERE ADVERSE EFFECTS

Require discontinuance of oral contraceptives and treat condition

1. Vascular disorders Thromboembolism

a. Venous thromboembolic disease

b. Myocardial infarction

c. Cerebrovascular disease strokes is in women over age 35.

2. Gastrointestinal disorders Many cases of cholestatic jaundice have been reported in patients taking progestin-containing drugs.

3. Depression

4. Cancer

Estrogen & Progesterone Inhibitors & Antagonists

TAMOXIFEN

Tamoxifen, a competitive partial agonist inhibitor of estradiol at the estrogen receptor,. It is extensively used in the treatment of breast cancer in postmenopausal women and is for chemoprevention of breast cancer in high-risk women.

CLOMIPHENE

Clomiphene is an older partial agonist, a weak estrogen that also acts as a competitive inhibitor of endogenous estrogens. It has found use as an ovulation-inducing agent

THE TESTIS (ANDROGENS & ANABOLIC STEROIDS, ANTIANDROGENS, & MALE CONTRACEPTION)

The testis, like the ovary, is controlled largely by the secretion of FSH High concentrations of testosterone locally are also required for continuing sperm production in the seminiferous tubules. With LH stimulation, testosterone is produced by the interstitial or Leydig cells found in the spaces between the seminiferous tubules.

Androgens & Anabolic Steroids

In humans, the most important androgen secreted by the testis is testosterone. In the normal male, testosterone or its active metabolite 5a-dihydrotestosterone is responsible for the many changes that occur in puberty. In addition to the general growth-promoting properties of androgens on body tissues, these hormones are responsible for penile growth. Changes in the skin include the appearance of pubic, axillary, and beard hair. The sebaceous glands become more active, The larynx grows and the vocal cords become thicker, leading to a lower-pitched voice. Skeletal growth stimulated and epiphysial closure accelerated. Other effects include growth of the prostate and seminal vesicles Androgens play an important role in stimulating and maintaining sexual function in men. Androgens increase lean body mass and stimulate body hair growth and sebum secretion.

Clinical Uses

A. Androgen Replacement Therapy In Men

B. Gynecologic Disorders.

C. Use As Protein Anabolic Agents

D. Anemia

E. Osteoporosis

F. Use As Growth Stimulators

G. Androgen Abuse In Sports

H. Aging

ANDROGEN SUPPRESSION & ANTIANDROGENS

Ketoconazole, used primarily in the treatment of fungal disease, is an inhibitor of adrenal and gonadal steroid synthesis.

Spironolactone, a competitive inhibitor of aldosterone competes with dihydrotestosterone for the androgen receptors in target tissues.

Finasteride.

Cyproterone .

cyproterone acetate.

Flutamide.

CHEMICAL CONTRACEPTION IN MEN

Tosterone and **Testosterone enanthate**, in a dosage of 400 mg per month, produced azoospermia in less than half the men treated.

Cyproterone acetate, produces oligospermia; however, it does not cause reliable contraception.

GOSSYPOL The drug has also been tried as an intravaginal spermicide contraceptive.

Chemotherapy Of Infections

Infection is a major category of human disease and skilled management of antimicrobial drugs is of the first importance.
The term chemotherapy is used for the drug treatment of infections in which the microorganism (viruses, bacteria, protozoa, fungi, worms) are destroyed or removed without injuring the host

Classification of antimicrobial drugs

Antimicrobial agents may be classified according to organism against which they are active
Antibacterial drugs
Antiviral drugs
Antifungal drugs
Antiprotozoal drugs
Anthelminthic drugs.

A few antimicrobials have useful activity across several of these groups. For example, metronidazole inhibits obligate anaerobic bacteria as well as some protozoa.)

Antimicrobial drugs have also been classified broadly into:

• **Bacteriostatic**

. those that act primarily by arresting bacterial multiplication, such as sulphonamides, tetracyclines and chloramphenicol

• **Bactericidal,**

those which act primarily by killing bacteria, such as penicillins, cephalosporins, aminoglycosides, isoniazid and rifampicin.

most bacteriostatic drugs can be shown to be bactericidal at high conc.

Bactericidal drugs act most effectively on rapidly dividing organisms. Thus a bacteriostatic drug, by reducing multiplication, may protect the organism from the killing effect of a bactericidal drug.

How antimicrobials act

Antimicrobials act at different sites in the target organism as follows:

The cell wall. This gives the bacterium its characteristic shape and provides protection against the much lower osmotic pressure of the environment.

Bacterial multiplication involves breakdown of the wall; interference with these processesprevents the organism from resisting osmotic pressures, so that it bursts. the drugs are effective only against growing cells. They include: penicillins, cephalosporins, vancomycin.

The cytoplasmic membrane inside the cell wall is the site of most of the microbial cell's biochemical activity. Drugs that interfere with its function include: polyenes (nystatin, amphotericin), azoles (fluconazole, itraconazole, miconazole), polymyxins

Protein synthesis. Drugs that interfere at various points with the build-up of peptide chains on the ribosomes of the organism include: chloramphenicol, erythromycin, fusidic acid, tetracyclines, aminoglycosides,

Nucleic acid metabolism Drugs may interfere•

directly with microbial DNA or its replication or repair, e.g. quinolones, metronidazole, RNA, e.g. rifampicin

indirectly on nucleic acid synthesis e.g. sulphonamides, rimethoprim.

Principles of antimicrobial chemotherapy

The following principles, many of which apply to drug therapy:

Make a diagnosis as precisely as is possible

Define the site of infection, the.

Decide whether chemotherapy is really necessary.

Select the best drug.

Administer drug in optimum dose, frequency, appropriate routes

Continue therapy until apparent cure has been achieved

Test for cure.

COMBINATIONS

Treatment with a single antimicrobial is sufficient for most infections. The indications for use of two or more antimicrobials are:

• To avoid the development of drug resistance,

• To broaden the spectrum of antibacterial activity:

• To obtain potentiation (or 'synergy'),

Problems with antimicrobial drugs

1-RESISTANCE

Mechanisms of resistance act as follows:

• Naturally resistant strains.

• Spontaneous mutation

• Transmission of genes from other organisms

Limitation of resistance to antimicrobials may be achieved by:

• ensuring that the indication, dose and duration of treatment are appropriate

• Using antimicrobial combinations in appropriate circumstances,

• Constant monitoring of resistance patterns in ahospital or community

• Restricting the use of the newest member of a group of antimicrobials so long as the currently-used drugs are effective; restricting use of a drug may become necessary where it promotes theproliferation of resistant strains.

2-SUPERINFECTION

When any antimicrobial drug is used, there is usually suppression of part of the normal bacterial flora of the patient which is susceptible to the drug. Often, this causes no ill effects, but sometimes a drug-resistant organism, freed from competition, proliferates to an extent which allows an infection to be established.

Antibiotic-associated (or Clostridium difficileassociated)colitis is an example of a superinfection. It is caused by alteration of the normal bowel flora, which allows multiplication of Clostridium difficile which releases several toxins which damage the mucosa of the bowel and promote excretion of fluid Mild cases usually respond to discontinuation of the offending antimicrobial allowing re-establishment of the patient's normal bowel flora. More severe cases treatment with oral metronidazole.

3-Opportunistic infection arises in patients whose immune systems are compromised Such infections involve organisms that rarely or never cause clinical disease in normal hosts

.

4- Masking of infection

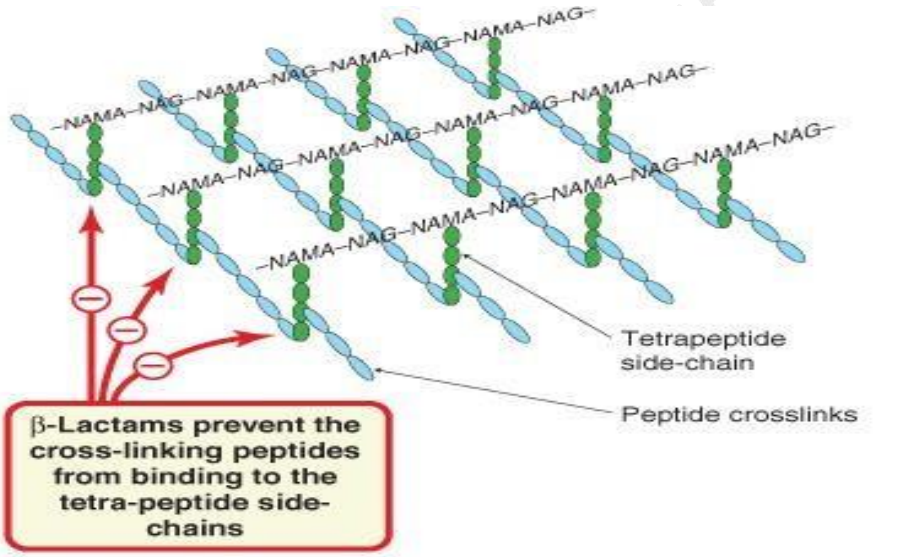
Masking of infections by chemotherapy is an important possibility. For example, a course of penicillin adequate to cure gonorrhoea may preventsimultaneously contracted syphilis from showing primary and secondary stages without effecting a cure.

Inhibition of cell wall synthesis

Inhibition of cell wall synthesis β –lactams

PENICILLINS

Penicillin act by inhibiting the enzymes (Penicillin Binding Proteins, PBPs) involved in the cross linking of the peptide glycan layer of the cell wall which protects the bacterium from its environment; Penicillin are thus bactericidal and are effective only against multiplying organisms because resting organisms are not making new cell wall.



Adverse effects.

The main hazard with the penicillins is *allergic reactions.* These include itching, rashesfever and Rarely (about 1 in 10 000) there is anaphylactic shock which can be fatal Other (nonallergic) adverse effects include diarrhea due to alteration in normal intestinal flora

Penicillins

are presented as their sodium or potassium, Physicians should be aware of this unexpected source of sodium or potassium, especially in patients with renal or cardiac disease. Extremely
high plasma penicillin concentrations cause convulsions.

Narrow Spectrum Penicillins

Benzylpenicillin (penicillin G)

Benzylpenicillin is highly active against *Streptococcus pneumoniae* and the Lancefield group A(β-haemolytic streptococcus *(Streptococcus pyogenes).*, Viridans streptococci are usually sensitive unless the patient has recently received penicillin.
for endocarditis Penicillin should be combined with an aminoglycoside,. This combination is synergistic.

. Benzylpenicillin is the drug of choice for infections
(**Anthrax),**
(Gas Gangrene)
(Tetanus)
(Diphtheria)
(Syphilis),
(Actinomycosis).

Preparations and dosage for injection.

Benzylpenicillin

may be given i.m. or i.v. in divided doses. When an infection is controlled, a change may be made to the oral route using Preparations for oral use.

Phenoxymethylpenicillin

(penicillin V), is resistant to gastric acid and so reaches the small intestine intact

Procaine penicillin,

given i.m. only, is a stable salt and liberates benzylpenicillin over 12-24 h, according to the dose administered.

Benzathine *penicillin*

is liberates benzylpenicillin over 21 day

Antistaphylococcal penicillins

Certain bacteria produce (β lactamases which open the (β lactama ring thus terminate the antibacterial activity.

Cloxacillin **flucloxacillin**

*(*resists β lactamases and resists degradation by gastric acid and is absorbed from the gut, but food markedly interferes with absorption..

Broad Spectrum Penicillins

The activity of these semi synthetic penicillins extends beyond Gram +ve and Gram- ve. As a general rule these agents less active than benzylpenicillin against Gram +ve cocci, but more active Gram - ve

Ampicillin

is moderately well absorbed when swallowed. The oral dose is 250 mg-1 g 6-8-hourly; or i.m. or i.v. 500 mg -6-hourly.. The drug is concentrated in the bile. Adverse effects. Ampicillin may cause diarrhoea but the incidence is less with amoxicillin.

Amoxicillin

is a better absorbed from the gut (especially after food), and for the same dose achieves double the plasma concentration. Diarrhoea is less frequent with amoxicillin than with ampicillin.

The oral dose is 250-500 mg 8-hourly; a parenteral form i.m. or i.v. 500 mg 6-8 hourly., however, amoxicillin is preferred because of its greater bioavailability and fewer adverse effects.

Co-amoxiclav (Augmentin).

Clavulanic acid is a β -lactam molecule which has little antibacterial activity but binds irreversibly to (β lactamases. Thereby it competitively protects the penicillin,

so potentiating it against bacteria which owe their resistance to production of β -lactamases, i.e. clavulanic acid acts as a 'suicide' inhibitor. It is formulated in tablets in combination with amoxicillin as co-amoxiclav.

Antipseudomonal Penicillins

Carboxypenicillins

have the capacity to destroy *Pseudomonas aeruginosa ,Proteus* spp.

Ticarcillin

(carboxypenicillins inactivate aminoglycosides)

if both drugs are administered in the same syringe or i.v infusion.

Ureidopenicillins

Their major advantages over the Carboxypenicillins are higher efficacy against *Pseudomonas aeruginosa* They are degraded by β lactamases.

Piperacillin. It is also available as a combination with the β -lactamase inhibitor tazobactam.

Cephalosporins

Mode of action is that of the (β -lactams, i.e Cephalosporins impair bacterial cell wall synthesis

Classification and uses. The Cephalosporins are categorised

TABLE 12.1 The cephalosporins

Drug	$t^{1}/_{2}$ (h)	Excretion in urine (%)	Comment
First generation			
Parenteral			
Cefazolin	2	90	May be used for staphylococcal infections but generally have been replaced by the newer cephalosporins.
Cefradine (also oral)	1	86	
Oral			
Cefaclor	1	86	All very similar. Effective against the common respiratory pathogens *Streptococcus pneumoniae* and *Moraxella catarrhalis* but (excepting cefaclor) have poor activity against *Haemophilus influenzae*. Also active against *Escherichia coli* which, increasingly, is demonstrating resistance to amoxicillin and trimethoprim. May be used for uncomplicated upper and lower respiratory tract, urinary tract and soft tissue infections, and also as follow-on treatment once parenteral drugs have brought an infection under control.
Cefadroxil	2	88	
Cefalexin	1	88	
Second generation			
Parenteral			
Cefoxitin (a cephamycin) (Cefotetan is similar)	1	90	More resistant to β-lactamases than the first-generation drugs and active against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Neisseria* spp., *Haemophilus influenzae* and many *Enterobacteriaceae*. Cefoxitin also kills *Bacteroides fragilis* and is effective in abdominal and pelvic infections. Cefuroxime may be given for community-acquired pneumonia, commonly due to *Strep pneumoniae* (not when causal organism is *Mycoplasma pneumoniae*, *Legionella* or *Chlamydia*). The oral form, *cefuroxime axetil*, is also used for the range of infections listed for the first-generation oral cephalosporins (above)
Cefuroxime (also oral)	1	80	
Cefamandole	1	75	
Third generation			
Parenteral			
Cefodizime	3	80	More effective than the second-generation drugs against Gram-negative organisms whilst retaining useful activity against Gram-postive bacteria. Cefotaxime, ceftizoxime and ceftriaxone are used for serious infections such as septicaemia, pneumonia, and for meningitis. Ceftriaxone also used for gonorrhoea and Lyme disease.
Cefotaxime	1	60	
Ceftazidime	2	88	
Ceftizoxime	1	90	
Ceftriaxone	8	56 (44 bile)	
Oral			
Cefixime	4	23 (77 bile)	Active against a range of Gram-positive and Gram-negative organisms including *Staphylococcus aureus* (excepting cefixime), *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Neisseria* spp., *Haemophilus influenzae* and (excepting cefpodoxime) many *Enterobacteriaceae*. Used to treat urinary, upper and lower respiratory tract infections.
Ceftibuten	2	65	
Cefpodoxime proxetil	2	80	

Adverse effects..

The most usual unwanted effects are allergic reactions of the penicillin type. There is cross-allergy between penicillins and Cephalosporins involving about 7-10 % of patients; .Pain at the sites of i.v. or i.m. injection .

If Cephalosporins are continued for more than 2 weeks, , haemolytic anaemia interstitial nephritis or abnormal liver function tests may occur especially at high dosage; these reverse on stopping the drug.

CARBAPENEMS

Members of this group have the widest spectrum
of all currently available antimicrobials, beingbactericidal against most Gram-positive and Gramnegative aerobic and anaerobic pathogenic bacteria.

They are resistant to hydrolysis by most P-lactamases.

Imipenem

Imipenem

Meropenem

Other inhibitors of cell wall synthesis

Vancomycin

acts on multiplying organisms by inhibiting cell wall formation at a site different from the (β- lactam antibacterials. It is bactericidal against most strains of *Staphylococcus aureus* (coagulase-negative staphylococci ,viridans group streptococci and enterococci, i.e. several organisms that cause endocarditis.

Vancomycin is poorly absorbed from the gut given i.v. for systemic infections, as there is no satisfactory i.m. preparation. It distributes effectively into body tissues and is eliminated by the kidney.

Uses. Vancomycin is effective in cases of antibiotic associated pseudomembranous colitis ((although oral metronidazole is preferred, being as effective and less costly)

Endocarditis in patients who are allergic to benzylpenicillin.

Adverse effects. The main disadvantage to vancomycin is auditory damage. Tinnitus and deafness may improve if the drug is stopped. Nephrotoxicity and allergic reactions also occur.

Teicoplanin is structurally related to vancomycin

It is used for serious infection including endocarditis, and for peritonitis t is less likely to cause oto- or nephrotoxicity than vancomycin,.

Inhibition of protein synthesis

Aminoglycosides

Mode of action. The aminoglycosides act inside the cell by binding to the ribosomes in such a way that incorrect amino acid sequences are entered into peptide chains. The abnormal proteins which result are fatal to the microbe.

Pharmacokinetics. are water soluble, Poor absorption from the GIT necessitates their administration i.v. or i.m. for systemic use.

Uses include:

Septicemia. Renal, Pelvic Abdominal Sepsis. Tuberculosis. Plague Bacterial Endocarditis . Brucellosis. Topical uses

Adverse effects.

toxicity is a risk when dose administered is high or of long duration,:

1- Ototoxicity.

2- Nephrotoxicity.

3- Neuromuscular blockade. Aminoglycosides may impair neuromuscular transmission

4- Other reactions include rashes, and hematological abnormalities.

INDIVIDUAL AMINOGLYCOSIDES

Gentamicin

Dose is 3-5 mg/kg body weight per day (the highest dose for more serious infections) as a single dose or in three equally divided doses.

Tobmmycin Amikacin Netilmicin Framycetin Streptomycin Spectinomycin

Tetracyclines

Mode of action.

Tetracyclines interfere with protein synthesis by binding to bacterial ribosome's and They are bacteriostatic.

Uses: Tetracyclines drugs of first choice for

Chlamydia rickettsiae, mycoplasma pneumonia, , Vibrio cholera use in acne.

Adverse reactions. Heartburn, nausea and vomiting due to gastric irritation are common, dizziness and other neurological reactions. Tetracyclines are selectively taken up in the teeth and growing bones of the fetus and of children, due to their chelating properties with calcium phosphate. This causes malformation, yellow or brown pigmentation and increased susceptibility to caries or fracture . the. tetracyclines be avoided in pregnancy to 12years of age

Interactions. Dairy products reduce absorption but antacids and iron preparations do much more, by chelating to calcium, and iron.

INDIVIDUALTETRACYCLINES

Tetracycline may be taken as representative of most tetracyclines The dose is 250-500 mg 6-hourly by mouth.

Doxycycline Minocycline. Demeclocycline. Oxytetracycline.

Macrolides

Erythromycin

binds to bacterial ribosome and interferes with protein synthesis; it is bacteriostatic and exhibits time-dependent bacterial killing.

Uses. Erythromycin is the drug of choice for:

• Mycoplasma pneumoniae in children, although in adults a tetracycline may be preferred

• Diphtheria (including carriers), pertussis and for some chlamydial infections

Dose is 250 mg 6-hourly or twice this in serious infection

Clarithromycin Clarithromycin is used for respiratory tract infections including atypical pneumonias and soft tissue infections.

Azithromycin

Sodium fusidate

A steroid antimicrobial which is used almost exclusively against (β-lactamase producing staphylococci; it has little useful activity against Gram-negative bacteria.

Uses.

avaluable drug for treating severe staphylococcal infections, including osteomyelitis and is available as i.v. and oral , an ointment or gel.

Adverse effects. It is well tolerated, but mild gastrointestinal upset is frequent. Jaundice may develop particularly with high doses

Chloramphenicol

Uses. The decision to use chloramphenicol for systemic infection is influenced by its rare but serious toxic effects Its role in meningitis and brain abscess has largely been superseded by cephalosporins, but it is asecond-line agent for these indications, and for **haemophilus epiglottitis** in children. Topical administration is effective for bacterial conjunctivitis.

Adverse effects

include gastrointestinal upset ,Optic and peripheral neuritis occur with prolonged use .The 'grey baby' syndrome occurs in neonates as circulatory collapse in which the skin develops a cyanotic grey color.

1. a dose-dependent, reversible depression of erythrocyte, platelet and leucocyte formation that occurs early in treatment (type A adverse drug reaction).
2. an idiosyncratic (probably genetically determined), non-dose-related, and usually fatal aplastic anaemia which tends to develop during, or even weeks after, prolonged treatment, and this has also occurred, rarely, with eye drops.

Clindamycin

(restricted in uses due to side effect of antibiotic associated pseudo membranous colitis)

Inhibition of nucleic acid synthesis

Sulphonamides and sulphonamide combinations

the successful chemotherapeutic agents Because of the risks of adverse drug reactions associated with their use, this is generally restricted to specific indications

MOA of sulphonamide combinations

he enzyme dihydrofolic acid (DHF) synthase converts(PABA) p- aminobenzoic acid to DHF which is subsequently converted to tetrahydric folic acid (THF), . purines and DNA.

The sulphonamides are structurally similar to PABA, successfully compete with it for DHF synthase and impair DNA formation.

. Trimethoprim acts at the subsequent step by inhibiting DHF reductase, which converts DHF to THF. The drug is relatively safe because bacterial DHF reductase is much more sensitive to trimethoprim than is the human form of the enzyme. Both Sulphonamides and trimethoprim are bacteriostatic.

CLASSIFICATION AND USES

Systemic use Sulphonamide-trimethoprim combination.

Cotrimoxazole(sulfamethoxazole plus trimethoprim);

the optimum synergistic in vitro effect against most susceptible bacteria is achieved with 5:1 ratio of sulfamethoxazole to trimethoprim,

The combination is, however, retained for:

• Prevention and treatment of pneumonia due to *Pneumocystis carinii,* a life-threatening infection in immunosuppressed patients

• Prevention and treatment of toxoplasmosis.

Topical application

Silver sulfadiazine is used for prophylaxis and treatment of infected burns, leg ulcers and pressure sores because of its wide antibacterial spectrum (which includes pseudomonads).

Adverse effects

include malaise, diarrhea,. Crystalluria may occur. Allergic reactions include: rash, fever, hepatitis, peripheral neuritis and Rarely, severe skin reactions including erythema multiforme (Stevens-Johnson syndrome) .Haemolysis may occur in G-6- deficient subjects.

Trimethoprim

The drug is rapidly and completely absorbed from the GIT is largely excreted unchanged in the urine. Trimethoprim is effective in treating urinary and respiratory tract infections due to susceptible organisms and for prophylaxis of urinary tract infections.

Adverse effects are fewer than with co-trimoxazole and include: skin rash, anorexia, nausea, vomiting, abdominal pain and diarrhoea.

Quinolones(4-quinolones, fluoroquinolones)

The first widely used quinolone, **Nalidixic acid**, was effective for urinary tract infections because it concentrated in the urine, but had little systemic activity. Fluorination of the quinolone structure was subsequently found to produce compounds that were up to 60 times more active than Nalidixic acid and killed a wider range of organisms.

MOA of quinolones

They act principally by inhibiting bacterial (but not human) DNA gyrase, so preventing the super coiling of DNA, a process that is necessary for compacting chromosomes into the bacterial cell;
they are bactericidal and exhibit conc-dependent bacterial killing.

Adverse effects

include gastrointestinal upset and allergic reactions (rash, pruritus, arthralgia, photosensitivity and anaphylaxis). CNS effects may develop with dizziness, headache and confusion,(contraindicated in pregnancy ,lactation ,child hood

Nalidixic acid

is now used principally for the prevention of urinary tract infection. It may cause haemolysis in glucose-6-phosphate dehydrogenase deficient subjects

Ciprofloxacin

is effective against a range of bacteria. Ciprofloxacin is indicated for use in infections of the urinary, gastrointestinal and respiratory tracts, tissue infections, gonorrhoea and septicaemia caused by sensitive organisms. The dose is 250-750 mg 12-hourly by mouth, 200-400 mg 12-hourly i.v infusion .

Norfloxacin

is used for acute or chronic recurrent UTI.

Ofloxacin

has modestly greater Gram positive activity,. It is indicated for urinary and respiratory tract infections and gonorrhoea.

Levofloxacin

has greater activity against Streptococcus pneumoniae than Ciprofloxacin and is used for respiratory and urinary infection.

Moxifloxacin has strong anti-Gram-positive activity, and may prove useful for respiratory tract infections including those caused by 'atypical pathogens Streptococcus pneumonia.

Azoles

This group includes:

• Metronidazole and tinidazole (antibacterial and antiprotozoal)

• Fluconazole, itraconazole, clotrimazole, econazole, ketoconazole, isoconazole and miconazole

• Albendazole, mebendazole and thiabendazole

Metronidazole

In obligate anaerobic microorganisms metronidazole is converted into an active form by reduction of its nitro group: this binds to DNA and prevent nucleic acid formation; it is bacteriostatic.Metronidazole is active against a wide range of anaerobic bacteria and also protozoa.

: **Dose.** by mouth 400 mg 8-hourly; ; or by i.v. infusion 500 mg 8-hourly. A topical gel preparation is present

Clinical indications are

1- Treatment of sepsis to which anaerobic organisms, postsurgical infection, intra-abdominal infection and septicaemia, wound and pelvic infection, osteomyelitis and abscesses of brain or lung
2- Antibiotic-associated pseudomembraneous colitis
3- Trichomoniasis of the urogenital tract in both sexes
4- Amoebiasis (Entameba histolytica), including both intestinal and extra-intestinal infection
5- Giardiasis (Giardia lamblia)
6- Acute ulcerative gingivitis and dental infections
7- Anaerobic vaginosis

Adverse effects

include headache, nausea, vomiting, diarrhoea, and an unpleasant metallic taste in the mouth; also, dizziness and ataxia.

Tinidazole

is similar to metronidazole but has a longer tl/2 The longer duration of action of tinidazole may be an advantage, e.g. in giardiasis, trichomoniasis and acute ulcerative gingivitis, in which tinidazole 2 g by mouth in a single dose is as effective as a course of metronidazole.

Antifungal Agents

Systemic Antifungal Agents for systemic infection

Amphotercin B, Flucytosine,, Griseofulvin,,Azoles (ketoconazole, miconazole, clotrimazole, itraconazole, fluconazole)

Topical Antifungal Agents

Nystatin,,Topical Azoles (Clotrimazole and Miconazole)

Helminthic infections

A. Ascariasis ,,Hookworm,, Pineworm infections

B. Hydatid disease.

Mebendazoles , Albendazoles , Niclosamide ,Piperazine

Drugs of Tuberculosis

--First –line Drugs of Tuberculosis:

Isoniazid (INH) The usual adult dose is 300 mg given once daily.

Rifampin, usually 600 mg/d orally, must be administered with isoniazid or other antituberculous drugs to patients with active tuberculosis to prevent emergence of drug-resistant mycobacteria.

Ethambutol ,Pyrazinamide , Streptomycin

--Alternative second line Drugs of Tuberculosis

(1) in case of resistance to first-line agents;

(2) in case of failure of clinical response to conventional therapy;

(3) in case of serious treatment-limiting adverse drug reactions;

(4) when expert guidance is available to deal with the toxic effects.

Cycloserine Amikacin Fluoroquinolones Azithromycin Carithromycin.

Drugs of Leprosy **Dapsone Rifampin**

Antiviral Agents **Acyclovir Zidovudine Lamivudine**

Anti – Influenza Agents **Amantadine**

Urinary Antiseptics. **Nitrofurantoin**

Antiparasitic Chemotherapy

Treatment of Malaria **Chloroquine , Primaquine Pyrimethamine**

Pyrimethamine, in combination with sulfadiazine, is first-line therapy in the treatment of toxoplasmosis.

Treatment of Amebiasis

Metronidazole ,Tinidazole ,Diloxanide furoate

Disinfectant Antiseptics

Alcoholes

Chlorhexidine

Halogens 1. Iodine 2. Chlorine

Phenolics

Aldehydes

Quaternary Ammonium compounds

Superoxidized Water

Peroxygen compounds hydrogen peroxide

Heavy Metals ,mercury and silver, are now rarely used disinfectants.

CANCER

Cancer is characterized by a shift in the control mechanisms that govern cell survival, proliferation, and differentiation..

CAUSES OF CANCER

The incidence, geographic distribution, and behavior of specific types of cancer are related to multiple factors, including sex, age, race, genetic predisposition, and exposure to environmental carcinogens.. Exposure to ionizing radiation has a significant risk factor for a number of cancers,Chemical carcinogens (particularly those in tobacco smoke) Viruses have implicated as etiologic agents of several cncers..

The Leukemias

1. Acute Leukemia Childhood Leukemia ALL

Adult Leukemia Acute Myelogenous Leukemia (AML)

2. Chronic Myelogenous Leukemia

3. Chronic Lymphocytic Leukemia

The Lymphomas

1. Hodgkin's Disease **2. Non-Hodgkin's Lymphomas**

Multiple Myeloma

Breast Cancer

Prostate Cancer **Gastrointestinal Cancers**

Lung Cancer **Ovarian Cancer Testicular Cancer**

Malignant Melanoma **Brain Cancer**

Clinical Pharmacology Of Cancer Chemotherapeutic Drugs

Cancer chemotherapy, as currently employed, can be curative in certain disseminated neoplasms.

In patients with widespread disseminated disease, chemotherapy provides only palliative rather than curative therapy at present

POLYFUNCTIONAL ALKYLATING AGENTS

Cyclophosphamide, melphalan, chlorambucil, busulfan, and, more recently, temozolomide

Nitrosoureas.

1. Procarbazine

2. Dacarbazine

3. Altretamine

4. Platinum Analogs

Cisplatin (cis-diamminedichloroplatinum [II])

Carboplatin is a second-generation platinum analog that exerts

.

ANTIMETABOLITES

Methotrexate **Pemetrexed**

Purine Antagonists 6-Thiopurines.. Fludarabine . Cladribine

Pyrimidine Antagonists

5-Fluorouracil Capecitabine Cytarabine Gemcitabine

Plant Alkaloids **Vinblastine** **Vincristine**

Epipodophyllotoxins

Two compounds, **(etoposide)** and a related drug, **(teniposide)**,

TAXANES **Paclitaxel** **Docetaxel**

.

ANTITUMOR ANTIBIOTICS

Anthracyclines **doxorubicin** and **daunorubicin**, **Idarubicin**

Mitoxantrone

Dactinomycin

Mitomycin

Bleomycin

HORMONAL AGENTS

Estrogen , Androgen Inhibitors

The antiestrogen **tamoxifen** has proved to be useful for the treatment of both early-stage , metastatic breast cancer **Flutamide** and **bicalutamide** used in combination with radiation therapy for the treatment of early-stage prostate cancer and in the setting of metastatic prostate cancer.

Gonadotropin-Releasing Hormone Agonists

Leuprolide and **goserelin** are synthetic peptide analogs of naturally occurring gonadotropin-releasing hormone (GnRH, LHRH)..

Aromatase Inhibitors

Aminoglutethimide.

Anastrozole

. **Letrozole** It is also indicated for first-line treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer and for second-line treatment of postmenopausal women with advanced breast cancer after progression on tamoxifen therapy.

Miscellaneous Anticancer Drugs

Imatinib

Imatinib It is indicated for the treatment of (CML),

Dasatinib (approved for use in CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL).

Growth Factor Receptor Inhibitors

1. Cetuximab

2. Gefitinib - Erlotinib

3. Bevacizumab

Asparaginase used to treat childhood acute lymphocytic leukemia.

Hydroxyurea used in chronic myelogenous leukemia and treatment of the blast crisis of acute myeloid leukemia

.**Retinoic Acid Derivatives** **All-trans-retinoic acid (tretinoin)**

Immunopharmacology

Agents that suppress immune system play an important role in preventing the rejection of organ or tissue grafts and in the treatment of certain diseases that arise from dysregulation of the immune response.

. Agents that augment the immune response or selectively alter the balance of various components of the immune system are important in the management of certain diseases such as cancer, AIDS, and autoimmune or inflammatory diseases.

The innate immune system is the first line of defense against an invading pathogen (antigen) and includes physical (eg, skin), biochemical (eg, complement, lysozyme, interferons), and cellular components (neutrophils, monocytes, macrophages, natural killer [NK], and natural killer-T [NKT] cells).

During the inflammatory response triggered by infection, neutrophils and monocytes enter the tissue sites from the peripheral circulation. This cellular influx is mediated by the release and action of **chemoattractant cytokines** from activated endothelial cells and immune cells (mostly tissue macrophages) at the inflammatory site. It is triggered by the adhesion of cell surface receptors on the immune cells to ligands on the activated endothelial cell surface. If these events occur successfully, the invading pathogen is ingested, degraded, and eliminated, and disease is either prevented or is of short duration.

The Adaptive Immune System

The adaptive immune system is mobilized from the innate response when the innate processes are incapable of coping with an infection. These include the ability to

(1) respond to a variety of antigens, each in a specific manner;

(2) discriminate between foreign ("non-self") antigens (pathogens) and self antigens of the host; and

(3) respond to a previously encountered antigen in a learned way by initiating a vigorous memory response.

This adaptive response culminates in the production of **antibodies**, which are the effectors of **humoral immunity;** and the activation of **T lymphocytes**, which are the effectors of **cell-mediated immunity.**

ABNORMAL IMMUNE RESPONSES

Hypersensitivity.

A. IMMEDIATE HYPERSENSITIVITY

1. Type I—

Type I hypersensitivity results from cross-linking of membrane-bound IgE on blood basophils or tissue mast cells by antigen. This cross-linking causes cells to degranulate, releasing substances such as histamine, leukotrienes, and eosinophil chemotactic factor, which induce anaphylaxis, asthma, hay fever, or urticaria (hives) in affected individuals (ingestion of certain foods, or drug hypersensitivity) requires immediate medical intervention.

2. Type II—

Hypersensitivity results from the formation of antigen-antibody complexes between foreign antigen and IgM or IgG immunoglobulins. example is a blood transfusion reaction that can occur if blood is not cross-matched properly. The disease is prevented in subsequent pregnancies by the administration of anti-Rh antibodies to the mother 24-48 hours aftar drlivary .

3. Type III—

Type III hypersensitivity is due to the presence of elevated levels of antigen-antibody complexes that deposit on basement membranes in tissues and vessels

B. TYPE IV: DELAYED-TYPE HYPERSENSITIVITY

Unlike type I, II, and III hypersensitivities, delayed-type hypersensitivity (DTH) is cell-mediated, and responses occur 2-3 days after exposure to the sensitizing antigen.

Autoimmunity

Autoimmune disease arises when ody mounts an immune response against itself due to failure to distinguish self tissues and cells from foreign (nonself) antigens Examples rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis.

Immunodeficiency Diseases

inadequate function in immune system; consequences include increased susceptibility to infections and prolonged duration and severity of disease. Immunodeficiency diseases are congenitally acquired or arise from extrinsic factors such as bacterial or viral infections or drug treatment. Affected individuals frequently succumb to infections caused by opportunistic organisms of low pathogenicity ofimmunocompetent host.

IMMUNOSUPPRESSIVE AGENTS

GLUCOCORTICOIDS.

IMMUNOPHILIN LIGANDS

1. Cyclosporine 2. Tacrolimus. 3. Sirolimus 4-Thalidomide

CYTOTOXIC AGENTS

1. Azathioprine 2. Cyclophosphamide 3. Leflunomide

4. Hydroxychloroquine is an antimalarial agent with immunosuppressant properties.

5. Other Cytotoxic Agents (**vincristine, methotrexate**, and **cytarabine**)

CLINICAL USES OF IMMUNOSUPPRESSIVE DRUGS

Solid Organ And Bone Marrow Transplantation

Autoimmune Disorders

IMMUNOMODULATION THERAPY

The development of agents that modulate the immune response rather than suppress it has become an important area of pharmacology. The rationale underlying this approach is that such drugs may increase the immune responsiveness of patients who have either selective or generalized immunodeficiency. The major potential uses are in immunodeficiency disorders, chronic infectious diseases, and cancer. The AIDS epidemic has greatly increased interest in developing more effective immunomodulating drugs.

Cytokines

Interferons

Cytokine Inhibitors

A more recent application of immunomodulation therapy involves the use of cytokine inhibitors for inflammatory diseases and septic shock.

Toxicology

Toxicology

the science that deals with the study of the adverse effects (toxicities) may produce in living organisms under specific conditions of exposure to chemicals or physical agents.

HOW DOES THE POISONED PATIENT DIE?

Many toxins depress **CNS** resulting in coma. Comatose patients frequently lose their airway protective reflexes and respiratory drive. Thus, they may die as a result of airway obstruction, respiratory arrest.

These are the most common causes of death due to overdoses of narcotics and sedative-hypnotic drugs Seizures, muscular hyperactivity, and rigidity may result in death

Cardiovascular toxicity is also frequently. Hypotension may be due to depression of cardiac contractility

hypovolemia resulting from vomiting, diarrhea.

Lethal arrhythmias can occur with overdoses of cardioactive drugs such as ephedrine, amphetamines, cocaine, digitalis, and theophylline;

Other organ system damage may occur after poisoning and is sometimes delayed in onset.

lung tissue, resulting in **pulmonary fibrosis**, beginning several days after ingestion.

Massive hepatic necrosis due to poisoning by acetaminophen or certain mushrooms results in hepatic encephalopathy and death 48-72 hours or longer after ingestion.

Management of the Poisoned Patient

Over a million cases of acute poisoning occur in the would each year, although only a small fraction are fatal. Most deaths are due to suicidal overdose by an adolescent or adult. Childhood deaths due to accidental ingestion of a drug or toxic household product
Even with a serious exposure, poisoning is rarely fatal if the victim receives prompt medical attention and good supportive care.

Attempting to the application of supportive measures that form the basis **("ABCDs")** of poisoning treatment.

Airway should be cleared of vomitus or any other obstruction and an oral airway or endotracheal tube inserted if needed.

Breathing. Patients with respiratory insufficiency should be intubated and mechanically ventilated.

Circulation continuous monitoring of pulse rate, blood pressure, urinary output, and evaluation of peripheral perfusion. An intravenous line should be placed and blood drawn for serum glucose and other routine determinations

.Every patient with altered mental status should receive a **Dextrose**, unless blood glucose test demonstrates that the patient is not hypoglycemic.

. HISTORY

Family members, police, and fire department or paramedical personnel should be asked to describe the environment in which the toxic emergency occurred and should bring to the emergency department any syringes, empty bottles, household products, or over-the-counter medications in the possibly poisoned patient

. PHYSICAL EXAMINATION

1. Vital signs Careful evaluation of vital signs (blood pressure, pulse, respirations, and temperature)

2. Eyes Constriction of the pupils (miosis) is typical of opioids, cholinesterase inhibitors (eg, organophosphate insecticides),

. Dilation of the pupils (mydriasis) is common with amphetamines, cocaine and atropine and other anticholinergic drugs..

3. Mouth The mouth may show signs of burns due to corrosive substances,. Typical odors of alcohol, hydrocarbon solvents, or ammonia may be noted..

4. Skin The skin often appears flushed, hot, and dry in poisoning with atropine and other antimuscarinics. Excessive sweating occurs with organophosphates, nicotine.

***5.* Abdomen** abdominal cramping, and diarrhea are common in poisoning with organophosphates, iron, arsenic, theophylline,.

6. Nervous system A careful neurologic examination is essential.

Decontamination

involves removing toxins from the skin or gastrointestinal tract.

Skin : Contaminated clothing should be completely removed and double-bagged to prevent illness in health care providers and for laboratory analysis. Wash contaminated skin with soap and water.

GASTROINTESTINAL TRACT

1. Emesis **2. Gastric lavage**

3. Activated charcoal." **4. Cathartics**

SPECIFIC ANTIDOTES

Specific antidotes reduce or abolish the effects of poisons through a variety of mechanisms, which may be categorised as follows:

• receptors, which may be activated, blocked or by passed

• enzymes, which may be inhibited or reactivated

• displacement from tissue binding sites

• exchanging with the poison

• replenishment of an essential substance

• binding to the poison (including chelating).

Methods of Enhancing Elimination of Toxins

it is important to consider whether measures for enhancing elimination, such as hemodialysis, Peritoneal dialysis or urinary alkalinization, forced diuretics can improve clinical outcome

TABLE 9.1 Some specific antidotes, indications and modes of action (see Index for a fuller account of individual drugs)

Antidote	Indication	Mode of action
acetylcysteine	paracetamol, chloroform, carbon tetrachloride	Replenishes depleted glutathione stores
atropine	cholinesterase inhibitors, e.g. organophosphorus insecticides	Blocks muscarinic cholinoceptors
	β-blocker poisoning	Vagal block accelerates heart rate
benzatropine	drug-induced movement disorders	Blocks muscarinic cholinoceptors
calcium gluconate	hydrofluoric acid, fluorides	Binds or precipitates fluoride ions
desferrioxamine	iron	Chelates ferrous ions
dicobalt edetate	cyanide and derivatives, e.g. acrylonitrile	Chelates to form nontoxic cobalti-and cobalto-cyanides
digoxin-specific antibody fragments (FAB)	digitalis glycosides	Binds free glycoside in plasma, complex excreted in urine
dimercaprol (BAL)	arsenic, copper, gold, lead, inorganic mercury	Chelates metal ions
ethanol	ethylene glycol, methanol	Competes for alcohol and acetaldehyde dehydrogenases, preventing formation of toxic metabolites
flumazenil	benzodiazepines	Competes for benzodiazepine receptors
folinic acid	folic acid antagonists e.g. methotrexate, trimethoprim	Bypasses block in folate metabolism
glucagon	β-adrenoceptor antagonists	Bypasses blockade of the β-adrenoceptor; stimulates cyclic AMP formation with positive cardiac inotropic effect
isoprenaline	β-adrenoceptor antagonists	Competes for β-adrenoceptors
methionine	paracetamol	Replenishes depleted glutathione stores
naloxone	opioids	Competes for opioid receptors
neostigmine	antimuscarinic drugs	Inhibits acetylcholinesterase, causing acetylcholine to accumulate at cholinoceptors
oxygen	carbon monoxide	Competitively displaces carbonmonoxide from binding sites on haemoglobin
penicillamine	copper, gold, lead, elemental mercury (vapour), zinc	Chelates metal ions
phenoxybenzamine	hypertension due to α-adrenoceptor agonists, e.g. with MAOI, clonidine, ergotamine	Competes for α-adrenoceptors (long-acting)
phentolamine	as above	Competes for α-adrenoceptors (short-acting)
phytomenadione (vitamine K_1)	coumarin (warfarin) and indandione anticoagulants	Replenishes vitamin K
pralidoxime	cholinesterase inhibitors, e.g. organophosphorus insecticides	Competitively reactivates cholinesterase
propranolol	β-adrenoceptor agonists, ephedrine, theophylline, thyroxine	Blocks β-adrenoceptors
protamine	heparin	Binds ionically to neutralise
Prussian blue (potassium ferric hexacyanoferrate)	thallium (in rodenticides)	Potassium exchanges for thallium
sodium calciumedetate	lead	Chelates lead ions
unithiol	lead, elemental and organic mercury	Chelates metal ions

Nicotine Poisoning

There are more than 4,000 chemicals in tobacco smoke Nicotine is the addictive drug that keeps you coming back for more.

Some of the other chemicals found in cigarettes

•Tar Carbon monoxide

• ammonia (household cleaning agent)

• acetone (nail polish remover)

• naphthalene (mothballs)

• methanol (rocket fuel)

• formaldehyde (which preserves the dead)

• phenol (disinfectant)

• hydrogen cyanide

• metals (76 metals including arsenic, cadmium, nickel)

• radioactive compounds (polonium-210)

• acetic acid (vinegar)

• toluene (industrial solvent)

From the moment that inhale tobacco smoke, it takes four seconds for the nicotine to reach blood stream and about ten seconds to reach the brain. Once the nicotine has attached itself to special sites in the brain, many relaxing chemicals are released. But this effect only lasts for a short time and then the addicted smoker needs to ‗top up' their nicotine. One of the reasons people continue to smoke is because they enjoy the effect of these relaxing chemicals being released by the brain.

The worst problem for tobacco smoke on health caused is that it is so addictive. include increased heart rate and blood pressure and constriction of blood vessels. Over time, ingestion of nicotine damage the lining of blood vessels and make blood platelets stickier. In combination these effects contribute to the development of heart disease.

Before developing a tolerance to nicotine, the smoker may experience mild effects of nicotine toxicity..

The average dose of nicotine from Nicotine Replacement Therapy (NRT is about one third to one half of that obtained from smoking. A person who is dependent on nicotine is extremely unlikely to experience any toxic effect from using NRT.

Most of the nicotine (80 per cent) is broken down in the liver. Nicotine is also filtered from the blood by the kidneys and removed in urine.

The nicotine in NRT) products, such as the patch, gum, lozenge, sublingual tablet or inhaler is safe if used according to the product directions.

Drug Interaction

There are several mechanisms by which drugs may interact, but most can be categorized as pharmacokinetic (absorption, distribution, metabolism, excretion), pharmacodynamic, or combined interactions.

Pharmacokinetic Mechanisms

The GIT **absorption** of drugs may be affected by concurrent use of other agents that

(1) have a large surface area upon which the drug can be adsorbed,
(2) bind or chelate,
(3) alter gastric pH,
(4) alter gastrointestinal motility, or
(5) affect transport proteins such as P-glycoprotein.

The drug interactions alter drug **distribution** include

(1) competition for plasma protein binding,
(2) displacement from tissue binding sites,
(3) alterations in local tissue barriers, eg, P-glycoprotein

The **metabolism** of drugs can be stimulated or inhibited by concurrent therapy.

Induction (stimulation) of cytochrome P450 in the liver and small intestine can be caused by drugs barbiturates, Carbamazepine, , phenytoin, rifampin,. Enzyme inducers can increase the activity of phase II metabolism such as Glucuronidation.

Inhibition of metabolism generally takes place more quickly than enzyme induction and may begin as soon as sufficient tissue concentration of the inhibitor is achieved. Drugs that may inhibit cytochrome P450 metabolism of other drugs include cimetidine, ciprofloxacin, clarithromycin, erythromycin, fluconazole, isoniazid, itraconazole, ketoconazole, metronidazole, , omeprazole.

The **renal excretion** of active drug can also be affected by concurrent drug therapy. The renal excretion of certain drugs that are weak acids or weak bases may be influenced by other drugs that affect urinary pH .

Pharmacodynamic Mechanisms

When drugs with similar pharmacologic effects are administered concurrently, an additive or synergistic response is usually seen. The two drugs may or may not act on the same receptor to produce such effects. Conversely, drugs with opposing pharmacologic effects may reduce the response to one or both drugs. Pharmacodynamic drug interactions are relatively common in clinical practice.

االهداف العامة :دراسه منهج علم االدوية وتأثيراتها على جسم الكائن الحي معرفه اساسيات علم االدويه والية عمل الدواء وحركيته داخل الجسم واالستخدمات العالجيه لمختلف االدوية حسب اجهزه الجسم وتاثيراتها العالجية والجانبية والجرع المستخدمة ودواعي وموانع االستخدام

Week	Theoretical subject	Practical
1	General aspects of Drugs Parmacology – Dose –Routes of Administration – Name and classification	Routes of administration Drugs
2	Pharmacodynamics -Drugs-receptors	Discusstion
3	Pharmacokinetics -–Absorption – Distribution –Metabolism-Excretion	Seminar
4	Drugs , Autonomic –N S - Neurotransmitters ,receptors	Absorption ,Excreation (Iodines ,Salicylates)
5	Cholinergic drugs Anticholinergic drugs , Ganglionic blocking drugs Neuromuscular blocking drugs	Discusstion
6	Adrenergic drugs Adrenergic α ,β blocking drugs	Seminar
7	C N S Depressant : Alcohol - Sedative hypnotics Benzodiazepine Barbiturate, Anticonvulsant,Antidepressant	Drugs antagonism Morphine and Nalorphine Curare –Physostigmine
8	C N S Stimulant drugs.	Discusstion
9	Anlgesic : Narcotin or Opioid -NSAIDs	Seminar
10	Anesthetics , General ,Local	Effect of parasympathetic drugs on glandular secreation
11	Drugs act on Respiratory system Bronchodilators ,Expectorants Anti-tussive ,Cold prepration	Discusstion
12	Drugs act on GIT , Anti ulcer Antaacid Antidiarrheal , Anti-emetic ,Laxative	Seminar
13	Diuretics ,classification ,mode of action	Evaution of analgesics
14	Cardio Vascular Drugs-Cardiac Glycosides ,Vasodilators-Antianginal ,Antiarrhrthmic drugs	Discusstion
15	Antihypertensive drugs ,-Drugs affect heamostasis ,Anticoagulant	Seminar

الفصل الدراسي الثاني

Week	Theoretical subject	Practical
1	Autocoids Prostaglandine , Histamine and Antihistamine ,Serotonine, Drugs used in gout treatment	Dose-Response Relationship
2	Vitamines : Water soluble vitamine- Fat soluble vitamine	Discusstion
3	Drugs influence metabolic,hormones Insulin and Antidiabetic agent	Seminar
4	Adrenal steroids ,Thyroid and antithyroid	Volatile aneasthetic
5	Anterior Pituitary ,Growth hormonrs ,gonadotrophine ,sex hormones Posterior Pituitary hormones ,oxytocinVasopressin	Discusstion
6	Contraception	Seminar
7	Introduction to Chemotherapy Antibiotic :Mechanism of action	Responce of human skin to Histamine and Antihistamine
8	Antibiotic: Inhibition of cell wall ,cell membrane	Discusstion
9	Antibiotic: Inhibition of proteins,nucleic acid synthesis	Seminar
10	Antiviral ,Antifungal, Antiamebiasis Antiparasitic , Anthelmintic, Antituberculosis and Disinfectant	Nicotine
11	Chemotherapy of neaplastic diseases	Discusstion
12	Principle of immunopharmacology	Seminar
13	Poison and antidotes Metal poisoning Plant poisoning	Heavy metal poisining Mercury poisining
14	General principle of poisoning treatment	Discusstion
15	Drugs interaction	Seminar

Routes of drugs administration

Pharmacokinetics is what the body does to drugs

The individual processes
(Absorption, Distribution , (Metabolism (biotransformation), Execration) Elimination.

Absorption

Considerations of anatomy, physiology, pathology, pharmacology, therapeutics and convenience determine the routes by which drugs are administered. Usually these are:

1-• *Interal :* by mouth (swallowed) or by sublingual or by rectum

2• *Parenteral:* by injection to intravenous or, intramuscular, subcutaneous or infusion.

3• *Other routes*, e.g. inhalation, topical application for local (skin, eye, lung) or for systemic (trans dermal) effect intrathecal, intradermal, intranasal, intratracheal, intrapleural, are used when appropriate.

Presystemic (first-pass) elimination.

drugs are metabolized in a single passage through the gut wall and (principally) the liver.

ADVANTAGES AND DISADVANTAGES OF ENTERAL ADMINISTRATION

Swallowing

-***Advantages*** are convenience , acceptability and economic

.***Disadvantages*** are that absorption may be delayed, reduced or even enhanced after food or slow or irregular after drugs that inhibit gut motility.. Some drugs are not absorbed and some drugs are destroyed in the gut

Sublingual or buccal administration

Advantages are that quick effect is obtained, e.g. with glyceryl trinitrate.

Disadvantages are the inconvenience if use has to be frequent, irritation of the mucous membrane and excessive salivation which promotes swallowing, so losing the advantages of by passing pre systemic elimination.

Rectal administration

.***Advantages*** are that a drug that is irritant to the stomach can be given by suppository (indomethacin); the route is suitable in vomiting, motion sickness, migraine or when a patient cannot swallow, and when cooperation is lacking (sedation in children).

Disadvantages psychological in that the patient may be refuced this route ,rectal inflammation may occur with repeated use and absorption can be unreliable, especially if the rectum is full of faece

ADVANTAGES AND DISADVANTAGES OF PARENTERAL ADMINISTRATION

Intravenous (bolus or infusion)

Advantages

Fast ,effective and highly predictable blood concentration and allows rapid modification of dose,. The route is suitable for administration of drugs that are not absorbed from the gut or are too irritant to be given by other routes.

Disadvantages

are the hazard if a drug is given too quickly, as plasma concentration may rise. . Local venous thrombosis is liable to occur with irritant formulations, especially if small veins are used. Infection of the intravenous catheter and the small thrombi on its tip are also a risk during prolonged infusions.

Intramuscular injection

Advantages

are that the route is reliable, suitable for irritant drugs, and depot preparations(hormonal contraceptives). Absorption is more rapid than following subcutaneous injection (soluble preparations are absorbed within 10-30 min).

Disadvantages

are that the route is not acceptable for self-administration, it may be painful, and if any adverse effects occur to a depot formulation, it cannot be removed.

Subcutaneous injection

Advantages is reliable and is acceptable for self-administration.

Disadvantages are poor absorption. Repeated injections at one site can cause lipoatrophy

By inhalation

Advantages are that drugs as gases can be rapidly taken up or eliminated, that has marked the use of this route in general anesthesia from its earliest days. Self-administration is practicable. provide high local concentration minimizing systemic effects.

Disadvantages special apparatus is needed (patients difficult use) drug must be nonirritant if the patient is conscious. Obstructed bronchi

Topical application

For local effect, e.g. to skin, eye, lung, anal canal, rectum, vagina.

Advantage high local concentration without systemic effect .

Disadvantage is that absorption can occur, especially when there is tissue destruction so that systemic effects result, e.g. adrenal steroids and neomycin to the skin, atropine to the eye. Ocular administration may cause systemic effects

For systemic effect. Transdermal delivery systems (TDS) release drug through a rate-controlling membrane into the skin and so into the systemic circulation. Fluctuations in plasma concentration associated with other routes of administration are largely avoided, as

is first-pass elimination in the liver. Glyceryl trinitrate stmenopausal hormone replacement therapy may be given by this way.

Distribution

If a drug is required to act throughout the body or to reach an organ , it must be go into the blood and into other body compartments. Most drugs distribute widely, part dissolved in body water, part bound to plasma proteins, in part to tissues. drugs bind selectively to plasma or tissue proteins or localised within ogans**.; the extent (amount) and strength (tenacity) of protein or tissue binding (stored drug) will affect its duration of action**

Metabolism

Metabolism is a general term for chemical transformations occur within the body and its processes change drugs by reducing lipid solubility to enhance elimination and alter a biological activity.

1. Conversion of a pharmacologically *active* to an *inactive*

2. Conversion of one pharmacologically *active* to another *active*

3 Conversion of a pharmacologically *inactive* to *active* sub *prodrugs*

THE METABOLIC PROCESSES

The liver is by far the most important drug metabolising organ, although a number of tissues, including the kidney, gut mucosa, lung and skin also contribute

Phase 1 metabolism a change in the drug molecule by oxidation, reduction or hydrolysis

Phase II water-soluble conjugate which is readily eliminated by the kidney . almost invariably terminates bilogical activity.

Dose:

Sub Therapeutic dose:

Therapeutic dose:

Minimum dose:

Maximum dose:

Toxic dose :

Fatal dose:

Median effective dose (ED50**):** the dose at which 50% of individuals exhibit the specified effect.

Median toxic dose (TD50): the dose required to produce a particular toxic effect in 50% of animals

Median lethal dose (LD50**):**

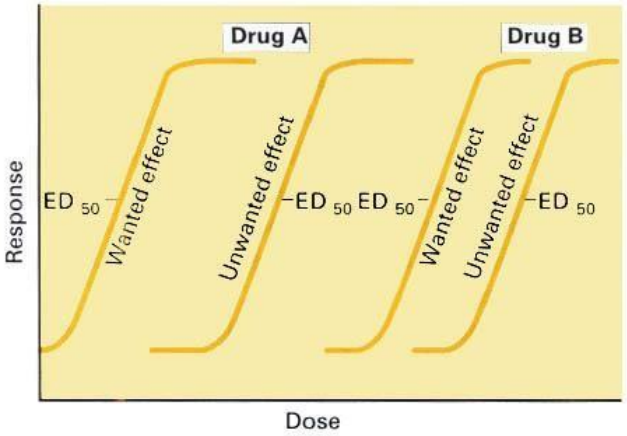
the dose required to produce death in 50% of animal

Duration of action :Time from beginning of drug action to end

Onset of drug action :Time from drug administration to appearance of action

T1/2 Time required to decrease drug amount in blood to half

Bioavailability:Fraction of unchanged drug in blood to dose administered .



ABSORPTION FROM THE GIT

The ***small intestine*** is the principal site for absorption of nutrients and it is also where most orally administered drugs enter the body.

The ***small intestine*** has attributes due to enormous surface area due to the intestinal villi, epithelium through which fluid readily filters in response to osmotic differences caused by the presence of food.

Absorption of drugs from the stomach does not play a major role in absorbing drugs, even those acidic and thus unionized and lipid-soluble at gastric pH, because its surface area is much smaller than that of the small intestine and gastric emptying is speedy (30 min).

FACTORS AFFECTING RATE OF ABSORPTION

Physicochemical Properties of Drugs and the Influence of pH

The ability of a drug to diffuse across membranes is frequently expressed in terms of its lipid–water partition coefficient .

This coefficient is defined as the ratio of the concentration of the drug in two immiscible phases: a nonpolar liquid representing the membrane and an aqueous buffer, usually at pH 7.4, representing the plasma .

The partition coefficient is a measure of the relative affinity of a drug for the lipid and aqueous phases.

Increasing the polarity of a drug, either by increasing its degree of ionization or by adding a carboxyl, hydroxyl, or amino group to the molecule, decreases the lipid–water partition coefficient.

The relationship between pH and degree of drug ionization is not linear that is, small changes in pH may greatly influence the degree of drug ionization,especially when pH and p*K*a values are initially similar.

Gastric Emptying Time

The rate of gastric emptying markedly influences the rate at which drugs are absorbed.(why)

Intestinal Motility

Increased gastrointestinal motility may reduce contact time in the upper portion of the intestine where most of drug absorption occurs. Conversely, a decrease in gastrointestinal motility may promote absorption by increasing contact time. Thus, the effect depends on the drug and change in motility

Food

Absorption of most drugs from the gastrointestinal tract is reduced or delayed by the presence of food in the gut. Drugs such as the tetracyclines, which are highly ionized, can complex with Ca__ions in membranes, food, or milk, leading to a reduction in their rate of absorption.

Formulation Factors

The ability of solid drug forms to dissolve and the solubility of the individual drug in the highly acidic gastric juice must be considered.

Drugs administered in aqueous solution are absorbed faster and more completely than tablet or suspension forms. Suspensions of fine particles (microcrystalline) are better absorbed than are those of larger particles.

ENTEROHEPATIC CIRCULATION

This system is illustrated by the bile salts, which are conserved by circulating through liver, intestine and portal blood about eight times a day. Enterohepatic recycling appears to help sustain the plasma concentration (in many oral contraceptives)

The presystemic metabolism

Drugs may be inactivated in the gastrointestinal tract, liver before they are absorbed. Drug metabolizing enzymes, such as the cytochrome P450 enzymes,play a major role in determining the extent of drug absorption of some drugs. Significant expression of cytochrome P450

3A4 and 3A5 occurs in the enterocytes lining the small intestine.These drug-metabolizing enzymes are responsible for approximately 50% of the cytochrome P450–mediated drug metabolism and thus can be expected to play a major role in the presystemic metabolism of a number of drugs.

ABSORPTION OF DRUGS FROM THE LUNG

The lungs serve as a major site of administration for a number of agents given for both local and systemic effects. Such drugs can be inhaled as gases (e.g., volatile anesthetics) or as aerosols (suspended liquid droplets or solid particles).

Absorption of agents from the lung is facilitated by the **large surface area of the pulmonary alveolar membranes (50–100 m2), the limited thickness of these membranes and the high blood flow to the alveolar region.**

Pulmonary absorption of volatile anesthetics across the alveolar–capillary barrier is very rapid because of the relatively high lipid–water partition coefficients

ABSORPTION OF DRUGS THROUGH THE SKIN

Most drugs that have been incorporated into creams or ointments are applied to the skin for their local effect.

The diffusion rate of a drug through the skin is largely determined by the compound's lipid–water partition coefficient. However, the stratum corneum, or outer layer of the epidermis, forms a barrier against the rapid penetration of most drugs. This is due in large part to the

relatively close-packed cellular arrangement and decreased amount of lipid in these cells. Thus, even highly lipid-soluble compounds will be absorbed much more slowly through the skin than from other sites.

The dermis, on the other hand, is well supplied with blood and lymph capillaries and therefore is permeable to both lipid-soluble and water-soluble compounds. If penetration of the skin by lipid-insoluble compounds does occur, it is probably accomplished by diffusion through the hair follicles, sweat glands, or sebaceous glands.

Distribution

If a drug is required to act throughout the body or to reach an organ, it must be got into the blood and into other body compartments. Most drugs distribute widely, in part dissolved in body water, in part bound to plasma proteins, in part to tissues. Distribution for drugs may bind selectively to plasma or tissue proteins or be localized within particular organs. Clearly, the site of localization of a drug is likely to influence its action, e.g. whether it crosses the blood-brain barrier to enter the brain; **the extent (amount) and strength (tenacity) of protein or tissue binding (stored drug) will affect the time it spends in the body and thereby its duration of action.**

Metabolism

Metabolism is a general term for chemical transformations that processes change drugs in two major ways:

1-REDUCING LIPID SOLUBILITY

Metabolic reactions tend to make a drug molecule progressively more water-soluble and so favors its elimination in the urine.

2-ALTERING BIOLOGICAL ACTIVITY

The end result of metabolism usually is the abolition of biological activity but various steps in the following consequences:

1. Conversion of a pharmacologically *active* to an *inactive* substance: this applies to most drugs.

2. Conversion of one pharmacologically *active* to another *active* substance: this has the effect of prolonging drug action.

3. Conversion of a pharmacologically *inactive* to an *active* substance, i.e. *prodrugs;* the effect may confer advantage or disadvantage.

THE METABOLIC PROCESSES

The liver is by far the most important drug metabolizing organ, although a number of tissues, including the kidney, gut mucosa, lung and skin also contribute. It is useful to think of drug metabolism in two broad phase

Phase 1 metabolism

brings about a change in the drug molecule by oxidation, reduction or hydrolysis The most important single group of reactions is the oxidations, in particular those undertaken by the so-called *mixed-function* (microsomal) *oxidases* which as the name indicates, are capable of metabolizing a wide variety of compounds.

The most important enzyme is a haem protein, *cytochrome P450* The many forms of cytochrome P450 enzymes (called isoenzymes19) are grouped into families CYP1,2 and 3. The family CYP3A is the most important, being involved in the biotransformation of the majority of all drugs; indeed CYP3A4 is expressed outside the liver and may be an important factor that explains poor oral availability of many drugs.

Phase II metabolism involves union of the drug with one of several polar (water-soluble) endogenous molecules that are products of intermediary metabolism, to form a water-soluble conjugate with glucuronide, acetylated. sulphates. Conjugation Phase II metabolism almost invariably terminates biological activity

Elimination

RENAL ELIMINATIONs . These processes normally maintain the fluid volume, electrolyte concentration, and pH of body fluids within a relatively narrow range. They remove waste products of cellular metabolism. A minimum daily urine output of approximately 400 mL is required to remove normal amounts of metabolic end products.

Glomerular Filtration

Arterial blood enters the glomerulus by the afferent arteriole at the relatively high pressure of approximately 70 mm Hg.This pressure pushes water, electrolytes, and other solutes outof the capillaries into Bowman’s capsule and then to the proximal tubule. This fluid, called glomerular filtrate, contains the same components as blood except for

blood cells, fats, and proteins that are too large to be filtered. The glomerular filtration rate (GFR) is about 180 L/day, or 125 mL/minute.

Tubular Reabsorption The term reabsorption, in relation to renal function, indicates movement of substances from the tubule (glomerular filtrate) to the blood in the peritubular capillaries.
Most reabsorption occurs in the proximal tubule, The remaining water and solutes are now called urine

Antidiuretic hormone from the posterior pituitary gland promotes reabsorption of water from the distal tubules and the collecting ducts of the kidneys. This conserves water needed by the body and produces more concentrated urine. Aldosterone, a hormone from the adrenal cortex, promotes sodium–potassium exchange mainly in the distal tubule and collecting ducts. Thus, aldosterone promotes sodium reabsorption and potassium loss.

Tubular Secretion

movement of substances from blood in the peritubular capillaries to glomerular filtrate flowing through the renal tubules
Secretion occurs in the proximal and distal tubules, across the epithelial cells that line the tubules. In the proximal tubule, uric acid, creatinine, hydrogen ions, and ammonia are secreted; in the distal tubule, potassium ions, hydrogen ions, and ammonia are secreted. Secretion of hydrogen ions is important in maintaining acid–base balance in body fluids.

FAECAL ELIMINATION When a drug intended for systemic effect is taken by mouth, a proportion may remain in the bowel and be excreted in the faeces.

Biliary excretion.

In the liver there is one active transport system for acids and one for bases, similar to those in the proximal renal tubule and there is a system that transports molecules, into the bile. that excreted in bile.

PULMONARY ELIMINATION

The lungs are the main route of elimination (and of uptake) of volatile anaesthetics

Drugs antagonism
Morphine and Nalorphine
Curare –Physostigmine

Cholinergic and anticholinergic Drugs

Stimulation of cholinoceptors in autonomic ganglia and at the postganglionic endings affects chiefly the following organs:

Eye: meiosis and spasm of the ciliary muscle occur so that the eye is accommodated for near vision. Intraocular pressure falls

Exocrine glands: there is increased secretion of the salivary, lachrymal, bronchial and sweat glands. The last are cholinergic, although anatomically part of the sympathetic system; some sweat glands, e.g. auxiliary, may be adrenergic.

Heart: bradycardia occurs with atrioventricular block and eventually cardiac arrest.

Bronchi: there is bronchoconstriction and mucosal hyper- secretion that may be clinically serious in asthmatic subjects, in whom cholinergic drugs should be avoided, as far as possible.

Gut: motor activity is increased and may cause colicky pain. Exocrine secretion is also increased. Tone in anal sphincters falls which may cause defecation

Bladder and ureters contract and the drugs promote micturition.

ALKALOIDS WITH CHOLINERGIC EFFECTS

Pilocarpine acts directly on end-organs innervated by postganglionic nerves (parasympathetic system plus sweat glands).

The chief clinical use of pilocarpine is to lower intraocular pressure in chronic simple glaucoma,; it produces miosis, opens drainage channels improves the outflow of aqueous humour. Oral pilocarpine is available for the treatment of xerostomia (dry mouth) in Sjogren's syndrome, or following irradiation of head and neck tumours. The commonest adverse effect is sweating.

ANTICHOLINESTERASES

Physostigmine is an alkaloid, acts for a few hours. Physostigmine is used synergistically with pilocarpine to reduce intraocular pressure. It has been shown to have some efficacy in improving cognitive function in Alzheimer-type dementia

Antimuscarinic drugs

Atropine

Atropine is an alkaloid from the plant (Atropa belladonna). In general, the effects of atropine are inhibitory but in large doses it stimulates the CNS. Atropine also blocks the muscarinic effects of cholinergic drugs both peripherally and on the central nervous system. The clinically important actions of atropine at parasympathetic postganglionic nerve endings are mostly the opposite of the activating effects on the parasympathetic system produced by acetylcholine and cholinergic drug It does not oppose cholinergic effects at the neuromuscular junction or significantly at the autonomic ganglia,.

Exocrine glands. All secretions except milk are diminished. Dry mouth and dry eye are common. Gastric acid secretion is reduced, Bronchial secretions are reduced

Smooth muscle is relaxed. In the gastrointestinal tract there is reduction of tone and peristalsis. Atropine relaxes bronchial muscle, an effect that is useful in some asthmatics. Micturition is slowed and urinary retention may be induced.

Ocular effects. Mydriasis occurs with a rise in intraocular pressure in eyes. An attack of glaucoma may be induced. The ciliary muscle is paralysed and so the eye is accommodated for distant vision.

Other antimuscarinic drugs

.

Homatropine is used for its ocular effects (1% and 2% solutions as eye drops). Its action is shorter than atropine

.

Therapeutic Applications

OPHTHALMOLOGIC DISORDERS, antimuscarinic agents, administered topically as eye drops or ointment, are very helpful in doing a complete examination .Antimuscarinic drugs should never be used for mydriasis unless cycloplegia or prolonged action is required

Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage ,also can occur without tissue

injury or evident disease and can persist after injury has healed.(Mild pain ,Moderate pain Severe pain, Over whelming acute pain)

TYPES OF PAIN

Acute pain ,Transient pain,Neuropathic,Chronic pain

Analgesic drug: a drug that relieves pain due to multiple causes, e.g. paracetamol, morphine., Analgesics are chosen according to the cause of pain and its severity..

• **Analgesics** are classed as **narcotic** (which act in the central nervous system and cause drowsiness, i.e. opioids) and **non-narcotic**(which act chiefly peripherally, e.g. diclofenac).

Narcotic or opioid analgesics

PRINCIPAL USES OF MORPHINE AND ITS ANALOGUES

• Relief of moderate to severe acute pain

• Premedication ,postoperative analgesia for surgery

• Symptomatic control of acute diarrhea, e.g. travelers" diarrhea (codeine)

• Suppression of cough (codeine)

• Production of euphoria as well as pain relief in the dying.

Classification of opioids by analgesic efficacy

Opioid efficacy	
Low efficacy for mild and moderate pain	**High efficacy for severe pain**
codeine	*buprenorphine
dihydrocodeine	dexromoramide
dextropropoxyphene	diamorphine (heroin)
*nalbuphine	dipipanone
*pentazocine	*meptazinol
	methadone
	morphine
	papaveretum
	pethidine (meperidine)
	phenazocine
	tramadol
*Partial agonist	

Nonsteroidal anti-inflammatory drugs (NSAIDs)

MODE OF ACTION

The members of this class of drug, although structurally heterogeneous, possess a mode of action which is to *block prostaglandin synthesis* ,., their key action of inhibiting prostaglandin formation is reflected in the range of effects, beneficial and adverse, which the members exhibit. NSAIDs may be categorized according to their COX specificity as:

• COX-2 *selective* compounds, whose selectivity for inhibiting COX-2 is at least 5 times that for COX- 1. The group includes *rofecoxib, celecoxib,meloxicam,* and *nabumetone.*

• *Non-COX-2 selective* compounds, which comprise all other NSAIDs. These drugs inhibit COX-1 as much as, or even more than, COX-2.

USES OF NSAIDs

.1- Analgesia: NSAIDs are effective for pain of mild to moderate intensity including musculoskeletal and postoperative pain, and inflammatory arthritis; they have the advantage of not causing dependence, unlike opioids

2-Anti-inflammatory action: this is utilized in all types of arthritis, musculoskeletal conditions.

3-Antipyretic action: PG synthesis in the hypothalamus is blocked, thus reducing fever.

4-Antiplatelet function: aspirin is indicated for the treatment and/or prevention of myocardial infarction, transient ischemic attacks and embolic strokes.

5-Prolongation of gestation and labour: inhibition of PG synthesis by the uterus during labour by indomethacin will prolong labour.

6-Primary dysmenorrhoea: mefanamic acid is used to reduce the production of PGs by the uterus which cause uterine hyper contractility and pain.

7-Further areas of potential benefit from NSAIDs are being explored, including the prevention of Alzheimer's dementia and colorectal carcinoma

TABLE 15.2 Nonsteroidal anti-inflammatory drugs licenced in the UK

Chemical class	Generic name	Compound	Half-life ($t^1/_2$)	Usual adult dose
Para-amino phenol	paracetamol	acetaminophen	2 h	1 g qid
Salicylic acids	aspirin	acetylsalicylic acid	15 min	300–900 mg q.d.s. maximum 4 g daily
	diflusinal	salicylate	7–15 h	500–1000 mg daily in 1 or 2 doses
	benorilate	salicylate-paracetamol ester		1.5 g q.d.s.
Acetic acids	indometacin	indole	4 h	initially 50–75 mg daily as 1 or 2 doses, maximum 200 mg daily
	acemetacin	indole	3 h	60 mg b.d. or t.d.s.
	sulindac	indene	8 h	200 mg b.d.
	diclofenac sodium	phenylacetic acid	2 h	75–150 mg daily in 2 divided doses
	etodolac	pyranocarboxyate	7 h	600 mg o.d.
	ketorolac	ketorolac trometerol	5h	
Fenamic acid	mefanamic acid	fenamate	3 h	500 mg t.i.d.
Propionic acids	ibuprofen	propionic acid	2 h	1.6–2.4 g daily in divided doses
	fenbufen	propionic acid	10 h	300 mg in a.m. and 600 mg nocte, or 450 mg b.d.
	fenoprofen	propionic acid	3 h	300–600 mg t.d.s. or q.d.s., maximum 3 g daily
	flurbiprofen	propionic acid	4 h	150–200 mg daily in divided doses, maximum 300 mg daily
	ketoprofen	propionic acid	1 h	100–200 mg in 2–4 divided doses
	naproxen	propionic acid	14 h	250–500 mg b.d.
	tiaprofenic acid	propionic acid	2 h	600 mg in 2–3 divided doses
Enolic acids	piroxicam	oxicam	45 h	20 mg o.d.
	meloxicam	oxicam	20 h	7.5–15 mg o.d.
	tenoxicam	oxicam	72 h	20 mg o.d.
	azapropazone	benzotriazine	18 h	1.2 g daily in 2 or 4 divided doses
	phenylbutazone	pyrazone	72 h	
Non-acid drugs	nabumetone	napthylalkanone	22 h	1 g nocte, additional 500 mg — 1 g o.d. if necessary
	celecoxib	coxib	10 h	200–400 mg daily in divided doses
	aceclofenac	phenylacetoxyacetic acid	4 h	100 mg b.d.
	rofecoxib	coxib	17 h	12.5–25 mg o.d.

االهداف العامة :دراسه منهج علم االدوية وتأثيراتها على جسم الكائن الحي معرفه اساسيات علم االدويه والية عمل الدواء وحركيته داخل الجسم واالستخدمات العالجيه لمختلف االدوية حسب اجهزه الجسم وتاثيراتها العالجية والجانبية والجرع المستخدمة ودواعي وموانع االستخدام
الفصل الدراسي الثاني

Week	Theoretical subject	Practical
1	Autocoids Prostaglandine , Histamine and Antihistamine ,Serotonine, Drugs used in gout treatment	Dose-Response Relationship
2	Vitamines : Water soluble vitamine- Fat soluble vitamine	Discusstion
3	Drugs influence metabolic,hormones Insulin and Antidiabetic agent	Seminar
4	Adrenal steroids ,Thyroid and antithyroid	Volatile aneasthetic
5	Anterior Pituitary ,Growth hormonrs ,gonadotrophine ,sex hormones Posterior Pituitary hormones ,oxytocinVasopressin	Discusstion
6	Contraception	Seminar
7	Introduction to Chemotherapy Antibiotic :Mechanism of action	Responce of human skin to Histamine and Antihistamine
8	Antibiotic: Inhibition of cell wall ,cell membrane	Discusstion
9	Antibiotic: Inhibition of proteins,nucleic acid synthesis	Seminar
10	Antiviral ,Antifungal, Antiamebiasis Antiparasitic , Anthelmintic, Antituberculosis and Disinfectant	Nicotine
11	Chemotherapy of neaplastic diseases	Discusstion
12	Principle of immunopharmacology	Seminar
13	Poison and antidotes Metal poisoning Plant poisoning	Heavy metal poisining Mercury poisining

14	General principle of poisoning treatment	Discusstion
15	Drugs interaction	Seminar

Dose-Response Relationship

DOSE RESPONSE RELATIONSHIP

it's the relation between the degree of response of biological system and the amount of toxicant or drugs (dose) administration . is related to

1- the dose

2- there is a receptor site with which the chemical interacts

3-the concentration at the site (related to dose administered)

Dose:

Sub Therapeutic dose:

Therapeutic dose:

Minimum dose:

Maximum dose:

Toxic dose :

Fatal dose:

Median effective dose (ED50**):** the dose at which 50% of individuals exhibit the specified effect.

Median toxic dose (TD50): the dose required to produce a particular toxic effect in 50% of animals

Median lethal dose (LD50**):**

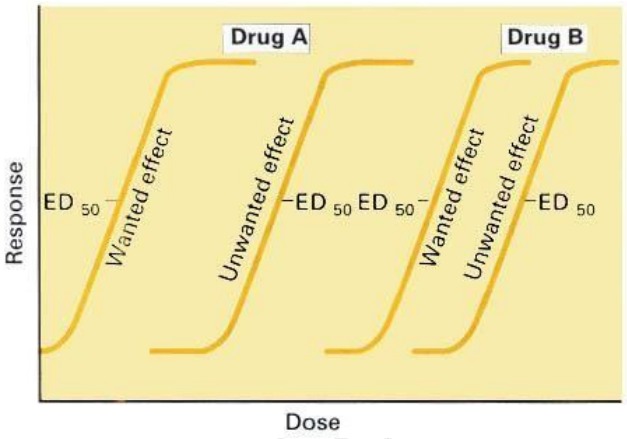
the dose required to produce death in 50% of animal

Duration of action :Time from beginning of drug action to end

Onset of drug action :Time from drug administration to appearance of action

T1/2 Time required to decrease drug amount in blood to half

Bioavailability:Fraction of unchanged drug in blood to dose administered .



When the dose of a drug is increased progressively, the desired response in the patient usually rises to a maximum beyond which further increases in dose elicit no greater benefit but induce only unwanted effects. This is because a drug does not have a single dose-response curve, but a different curve for *each action*, wanted as well as unwanted. unwanted actions are recruited if dose is increased after the maximum therapeutic effect. the concept of the therapeutic index

or ratio as the maximum tolerated dose divided by the minimum curative dose

Different responses

Individuals may vary considerably in their responsiveness to Drug; a single individual may respond differently to the same drug at different times during the course of treatment.

The idiosyncratic are usually caused by genetic differences in metabolism of the drug or by immunologic mechanisms, including allergic reactions. An individual patient is **hypo reactive** or **hyperactive** to a drug in that the intensity of effect of a given dose of drug is diminished or increased in comparison to the effect seen in most individuals.

Inhalation anaesthetics

The preferred inhalation agents are that are minimally irritant and non flammable**, nitrous oxide** and the fluorinated hydrocarbonse **Halothane**, **Isoflurane** , **Sevoflurane**, **Enflurane** ,. **Desflurane**)

HISTAMINE

Histamine exerts its biologic actions by combining with specific cellular receptors located on the surface membrane. The four different histamine receptors thus far characterized are designated H_1 -H_4

H1 Smooth muscle ,Endothelium ,Brain
H2 Gastric mucosa, cardiac muscle, mast cells, brain
H3 Presynaptic: brain, myenteric plexus, other neurons
H4 Eosinophils, neutrophils, CD4 T cells

CLINICAL PHARMACOLOGY OF HISTAMINE

In pulmonary function laboratories, histamine aerosol has been used as a provocative test of **bronchial hyperreactivity**..
Histamine should not be given to patients with asthma (except as part of a carefully monitored test of pulmonary function) or to patients with active ulcer disease or gastrointestinal bleeding.

Beta hestine is histamine analoge used in meniere-s disease

Histamine Antagonists

H_1-Receptor Antagonists

A. Allergic Reactions.
B. Motion Sickness And Vestibular Disturbances
C. Nausea And Vomiting Of Pregnancy

H_2-Receptor Antagonists
H_3- H_4-Receptor Antagonists
Although no selective H_3 or H_4 Antagonists are presently available for clinical use,. H_3-selective ligands may be of value in sleep disorders, obesity, and cognitive and psychiatric disorders. H_4 blockers have potential in chronic inflammatory conditions such as asthma

Nicotine Poisoning

There are more than 4,000 chemicals in tobacco smoke Nicotine is the addictive drug that keeps you coming back for more.

Some of the other chemicals found in cigarettes

•Tar Carbon monoxide

• ammonia (household cleaning agent)

• acetone (nail polish remover)

• naphthalene (mothballs)

• methanol (rocket fuel)

• formaldehyde (which preserves the dead)

• phenol (disinfectant)

• hydrogen cyanide

• metals (76 metals including arsenic, cadmium, nickel)

• radioactive compounds (polonium-210)
• acetic acid (vinegar)
• toluene (industrial solvent)

From the moment that inhale tobacco smoke, it takes four seconds for the nicotine to reach blood stream and about ten seconds to reach the brain. Once the nicotine has attached itself to special sites in the brain, many relaxing chemicals are released. But this effect only lasts for a short time and then the addicted smoker needs to ‘top up’ their nicotine. One of the reasons people continue to smoke is because they enjoy the effect of these relaxing chemicals being released by the brain.

The worst problem for tobacco smoke on health caused is that it is so addictive. include increased heart rate and blood pressure and constriction of blood
vessels. Over time, ingestion of nicotine damage the lining of blood vessels and make blood platelets stickier. In combination these effects contribute to the development of heart disease.

Before developing a tolerance to nicotine, the smoker may experience mild effects of nicotine toxicity..

The average dose of nicotine from Nicotine Replacement Therapy (NRT is about one third to one half of that obtained from smoking. A person who is dependent on nicotine is extremely unlikely to experience any toxic effect from using NRT.

Most of the nicotine (80 per cent) is broken down in the liver. Nicotine is also filtered from the blood by the kidneys and removed in urine.

The nicotine in NRT) products, such as the patch, gum, lozenge, sublingual tablet or inhaler is safe if used according to the product directions.

Heavy Metal Intoxication and Chelators

Some metals such as iron are essential for life, while others such as lead are present in all organisms but serve no useful biologic purpose.When intoxication occurs, chelator molecules may be used to bind the metal and facilitate its excretion from the body.

MERCURY

Metallic mercury the only metal that is liquid under ordinary conditions. industrial and commercial applications found in the electrolytic production of chlorine and caustic soda; the

manufacture of electrical equipment, **thermometers**, fluorescent lamps; **dental amalgam**; and gold production. Use in pharmaceuticals and in biocides has declined, but occasional use in **antiseptics** is still encountered..

Mercury **interacts with sulfhydryl groups in vivo**, **inhibiting enzymes and altering cell membranes.**.

Treatment

A. ACUTE EXPOSURE

In addition to intensive supportive care, prompt chelation with oral or intravenous unithiol, intramuscular dimercaprol, or oral succimer may be of value in diminishing nephrotoxicity after acute exposure to inorganic mercury salts.

B. CHRONIC EXPOSURE

. Dimercaprol has been shown to redistribute mercury to the central nervous system from other tissue sites, and since the brain is a key target organ, dimercaprol should not be used in treatment of exposure to elemental or organic mercury. Limited data suggest that succimer, unithiol, and N-acetyl-L-cysteine (NAC) may enhance body clearance of methylmercury.

PHARMACOLOGY OF CHELATORS

Chelating agents are drugs used to prevent or reverse the toxic effects of a heavy metal on an enzyme or other cellular target, to accelerate the elimination of the metal from the body.

SUCCIMER	**DIMERCAPROL**
EDETATE CALCIUM DISODIUM	**DEFEROXAMINE**
PENICILLAMINE	**UNITHIOL**