Lecture notes in clinical Pharmacology

Prepared by

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1. Introduction to Pharmacology

The Drug

Generally, a drug is any chemical agent that interacts with living Processes and used because of this action in the treatment, Prevention or diagnosis of disease (biologically active substance)

Treatment **could be: curative** (as antibiotics in bacterial infections) **or suppressive** (as in treatment of hypertension, diabetes, epilepsy..

Prevention**:** e.g. malaria, Tb contacts, aspirin after myocardial infarction

Diagnosis**:** e.g. edrophonium (short-acting anticholinesterase) in the diagnosis of myasthenia gravis

Sources of drugs

A drug may occur **naturally** in animals e.g. insulin or plants: e.g. Morphine from opium

It may be **semi-synthetic** e.g. aspirin from salicylates or **wholly synthetic** e.g. phenobarbitone and most recent drugs

An ideal drug should have:

- a very selective action
- no side effect or toxicity
- easily administered preferably orally
- effective for the appropriate period

A drug should pass through 4 filters before being prescribed for The patients:

- **Efficacy** (Is it efficacious? If yes…)
- **Safety** (Is it safe? If yes …)
- **Suitability** (Is it suitable to be administered?)

- **Cost** (it should not be expensive)

Drugs are <u>rarely highly selective</u> for one system. For this reason, they have:

- **<u>a main effect</u>** i.e. the one we wish to use therapeutically
- **<u>Side effects</u>** are undesirable in a particular condition.

These side effects could be:

- **harmless** (e.g. red discoloration of urine by rifampicin)
- **harmful (adverse)** e.g. aplastic anemia, bleeding, …

Serious side effects that have adverse consequences on the subjects and may even cause death are called **<u>toxic effects</u>**

<u>Drug action</u>: is the initial drug combination with cellular components (enzymes, membrane or other functional components)

<u>Drug effects</u>: is the biochemical or physiological changes resulting from its action

<u>Examples</u>: Drugs can bind and block D2-receptors in the chemoreceptor trigger zone (drug action). This can stop vomiting – antiemetic (drug effect)

<u>Pharmacology</u>

Is the science that deals with the properties and effects of drugs including their mechanism of action?

The <u>two main aspects</u> of pharmacology are:

- **<u>Pharmacodynamics</u>:** is the study of biochemical and physiological effects of the drug on the body including its mechanism of action
- **<u>Pharmacokinetics</u>:** is the study of the effect of the body on the drug in terms of absorption, distribution, metabolism and excretion.

<u>Toxicology</u>: is the science of poisons and poisoning. It is a branch of pharmacology that deals with the undesirable effects of drugs and other chemicals on living systems.

Pharmacy:

is concerned with the preparation and dispensing of drugs

Substandard Drugs

A drug is called a substandard drug when the composition of a drug product does not conform to the correct scientific specifications.

Such a drug can be **ineffective** leading to exacerbation of the patient's condition or **toxic**, and both can be fatal

Substandard products may be caused by:

- human error (defective batch) (unintentional)

-counterfeiting (fake drugs) (intentional)

Counterfeit medicines:

The WHO defines counterfeit pharmaceutical product as (one which is **deliberately** and **fraudulently** mislabeled with respect to identity and/or source).

Examples: Look-alike products may contain:

- little or no active ingredient
- possibly contain harmful ingredients
- relabeled medications that have expired but have been repackaged and remarketed with a much later expiration date.

Magnitude of the problem

The WHO has estimated that 10% of global pharmaceutical sales involve counterfeit drugs. In countries with weak regulatory authorities (e.g. developing countries), counterfeit medicines may comprise 20-50% of available products.

Essential Drugs

The WHO issues every few years a list of essential drug list i.e.

drugs that satisfy the health care needs of the majority of the population and should, therefore, be available at all times in adequate amounts and in the appropriate dosage forms.

Antituberculosis medicines

- **Ethambutol**
- **Isoniazid**
- **Pyrazinamide**
- **Rifampicin**
- **Streptomycin**

2. Drug discovery and development

Introduction

Knowledge of drug discovery and development is likely better to inform the prescriber of the safety, efficacy and economics of using new drugs and treatments.

The knowledge of drug development among qualified doctors was disappointingly poor, only 32% of doctors know about drug development

(Reference: British Journal of Clinical Pharmacology, 2005)

Objective of the lecture

To clarify the key features of drug development, from the discovery process to pharmacovigilance, these steps include preclinical and clinical testing as well as evaluation of safety, efficacy and clinical effectiveness.

I. Drug discovery:

New drugs can be discovered by one of the following methods:

(reference: Clinical Pharmacology, by PN Bennett and MJ Brown, 10th edition, 2008, page 32)

1. Molecular modeling: this can be done with the help of three dimensional computer aided design to build up a molecule from a known molecule. This will help to:
    a. enhance efficacy and to minimize side effect
    b. Create highly selective compound that targets a specific receptor.
2. Combinatorial chemistry: this involves random mixing of compounds to produce sets of new compounds. This method can generate billions of compounds which can be screened by fully automated robotic systems. If the compound passes the test then it can be transferred to further steps of evaluation. Important Note: (you may generate 5000-10,000 molecules to produce one successful new drug)

3. Biotechnology: This involves the use of recombinant DNA technology or genetic engineering. This technique is used to clone and express human genes in bacteria (E-coli) or yeast to produce insulin.
   Example of this technique: growth hormone, erythropoietins, interferons and others.

II. Older approaches for drug discovery:

This approach is still in use and includes:

a. Animal model of human disease; for example inducing diabetes in animal model and testing drugs activity in this disease**.**
b. Screening natural products.
c. screening for new uses of drugs already in use in therapy; e.g. aspirinas antithrombotic (aspirin is one of the old analgesic and antipyretic drug).

When a compound (drug) passed the initial screening tests it must be carefully evaluated for potential risks before clinical testing. This can be accomplished in animal models by the following steps:

A. preclinical safety and toxicity testing: this test involves testing the drug in **animals** to determine the following parameters:

1. **Pharmacodynamic effects**: to investigate the proposed action of the drug in the animal and to monitor undesirable pharmacodynamics effects.
2. **Pharmacokinetics**: to study, in animals, absorption, distribution, metabolism and elimination, and also to relate these parameters to human
3. **Toxicology**: This test is described in **(table 1)**.

Table 1. Toxicology and safety testing

Type of test	Approach
Acute toxicity	**Acute dose that is lethal in approximately 50% of animals (LD50). Determine maximum tolerated dose. Usually 2 species, 2 routes, single dose are used**
Sub-acute toxicity	**Three doses, 2 species. Up to six months testing**
Chronic toxicity	**1 to 2 years testing**
Effect on reproductive system	
Carcinogenic potential	**2 years, 2 species are required**
Mutagenic potential	

From the preclinical safety and toxicity testing the following parameters can be obtained:

1. Determination of the "no effect" dose.
2. Maximum dose at which the specified toxic effect is not seen.
3. Smallest dose that is observed to kill any animal
4. Median lethal dose (LD50), the dose that kills approximately 50% of the animals
5. Therapeutic index (TI) which is the ratio between LD50 and ED50 (dose effective in 50% of diseased animals); TI= LD50/ED50

A therapeutic index equal to 1; this means that LD50 =ED50 and this compound is a poison rather than a drug. However, when TI, for example, equals 10 this means that the lethal dose is 10 times the therapeutic dose; thus, the higher the TI, the more safe the drug is.

6. calculation of the initial doses to be tried in humans; the doses are usually taken as 1/100 – 1/10 of the no-effect dose.

III. Limitations of animal toxicities studies(Ref: Katzung Basic and clinical Pharmacology, 2006)

1. Time consuming and expensive (it is estimated that the cost of preclinical and toxicology studies is $41 million per successful drug)
2. Large number of animals must be used
3. Extrapolation of toxicity data from animals to human are not completely reliable because of species variation.
4. Rare adverse effects are unlikely to be detected

Clinical studies on human:

There are terms which should be known to the students before going through the clinical studies on human, these are:

Term	Explanation
Single-blind study	A clinical trial in which the investigators –but not the subjects know which subjects are receiving active drug and which are receiving placebos
Double-blind study	A clinical trial in which neither the subjects nor the investigators know which subjects are receiving placebos; the code is held by a third party
placebo	An inactive “dummy” medication made up to resemble the active investigational formulation as much as possible
Positive control	A known standard therapy, to be used along with placebo to fully evaluate the safety of a new drug in relation to the others available drugs
mutagenic	An effect on the inheritable characteristics of a cell or organism – a mutation in the DNA; tested in microorganism with the “Ames test”
Teratogenic	An effect on the development of an organism resulting in abnormal structure or function; not generally heritable
carcinogenic	An effect of inducing malignant characteristics

Clinical studies on human for new drugs should be done on human to evaluate safety and efficacy: The drug should pass through four phases: (Clinical pharmacology, 2008, P.N. Bennet, M.J. Brown)

Phase I: This phase is usually done on normal volunteers or volunteer patients (20-50 subjects); to test for:

a. Pharmacokinetics

b. Pharmacodynamics (biological effects)

c. Safety and efficacy.

Phase II: Patients (50-300 patients) to test for efficacy

Phase III: Patients (250-1000 and more); randomized controlled clinical trial to test for safety and efficacy and comparison with other drugs.

Phase IV: patients (2000 – 10 000) to study pharmacovigilance (post Licensing studies), safety and efficacy.

The average cost is around **$100 million** are involved in the development of a single new drug.

3. Mechanism of Drug Action

I. Mechanisms of drug action:

1. Receptor occupation as cholinergic, adrenergic and histamine receptors, occupied by acetylcholine, adrenaline and histamine respectively
2. Interference with ion channels, some drugs act directly on ion channels and alter their function as local anesthetics act by blocking Na^+-channels.
3. Inhibition of membrane bound enzymes as Na^+/K^+ ATP-ase inhibition by digoxin.
4. Through physicochemical properties; like osmotic effect as magnesium sulphate, a laxative acts by increasing water in the faecal material and facilitate their passage through the colon, manitol acts as osmotic diuretic
5. Direct chemical reaction as the use of alkaline to neutralize gastric acid in the stomach and Chelating agents as penicillamine in heavy metals poisoning.
6. Enzyme inhibition as cholinesterase inhibition by nesostigmine and angiotensin converting enzyme inhibition by captopril.
7. Antimicrobials cause inhibition of bacterial metabolic processes as sulphonamides inhibit bacterial dihydrofolate reductase enzyme, this leads to inhibition of folic acid synthesis by the bacteria, but not affects the human which does not synthesize folic acid.
8. Carrier mechanism: some drugs act by interfering with passage of molecules across the cell membrane such as the inhibition of noradrenaline uptake by tircyclic antidepressants, carrier mechanism is

important for the transport of molecules as glucose, amino acids and organic molecules.

Receptors: are protein macromolecules usually but not always situated on the cell membrane and have the ability to combine with the drug molecule, and transmit the drug effect to the inside of the cell. The drug molecule has to be similar in size, shape, chemical structure in order to combine to its specific receptor. So the receptors are important for the specific and selective action of the drug.

The presence of receptors usually indicates that there are endogenous substances of similar shape that can combine to these receptors such as endogenous opiates that bind to opiates receptors, adrenaline and noradrenaline that combine to adrenoceptors.

II. Mechanisms of drug binding to receptors:

1. Covalent binding : are strong and usually irreversible bonds and rarely mediate drug effect as cytotoxic drugs.
2. Electrostatic bonds: are more common than covalent binding.
3. Hydrophobic bonds: are usually weak bonds and are important in highly lipid soluble drugs binding with the lipids cell membranes.

Receptors can be divided into three different types:

1. Receptors linked to ion channels: these receptors regulate the flow of ions across their channels in the cell membrane example; nicotinic cholinergic receptors and Na^+ ion channels, GABA receptors and Cl^- ion channels. They are activated in milliseconds.
2. G-protein coupled receptors: these receptors are linked to G protein which mediates the intracellular action by binding to guanosine triphosphate. This will lead to the activation of a second messenger mechanism called adenylcyclase which results in the production of

cyclic-adenosine monophosphate(cAMP), and this regulates protein phosphorylation. They act in seconds to minutes, as the beta-adrenoceptors.

3. Intracellular receptors; these receptors are located inside the cell and therefore the drug molecule must diffuse to the inside of the cell to interact with these receptors as in estrogen receptors which are located in the nucleus of the cell and they stimulate DNA and proteins synthesis and usually take hours to act, also corticosteroids have similar receptors

III. Second messenger : The second messenger is an intracellular component that can transmit the effect of the drug to the inside of the cell following receptor stimulation, such as cyclic adenosine monophosphate (c-AMP) and calcium ions, changes in this second messenger will produce the drug effects as muscle contraction or relaxation or gland secretion.

A. Receptors regulations: The response to drug depends on the number of receptors occupied. The number of receptors may be affected by the continued presence of the drug. In general, the number of receptors declines with continuous agonist drug administration and this will lead to decrease in drug response (receptors down-regulation) this is in order to protect the cell from excessive stimulation. The reduction in receptors occurs by the process of endocytosis, which means that the cell engulfs the receptors and degrades it.

B. Tachyphylaxis: rapid reduction in the response to the drug following repeated administration (this is due to receptors down-regulation). Continuous administration of the antagonist will increase the number of receptors (receptors up-regulation), which makes sudden

withdrawal of the antagonist dangerous after prolonged use as beta-blockers

C. Dose response relation

The effect produced by a drug is generally a function of the amount of the drug administered "dose-Response Curve". The magnitude of the drug effect depends on its concentration at the receptor site, which is in term determined by the dose of the drug administered and affected by factors related to the drug characteristics and the pharmacokinetics parameters.

D. Dose-Response Curve:

As the concentration of the drug increases, the magnitude of its pharmacological effect will also increase (i.e. increasing the drug amount will increase the response). The curve has S shape with a linear part in the middle.

a. Quantal-dose response (dose percent effect): for determination of drug response in the population, it is used for all or none effect as prevention of convulsion, cardiac arrhythmias and in acute toxicity studies.

Therapeutic index is the ratio of toxic dose to the effective dose

Therapeutic index = toxic dose / effective dose

Therapeutic index is a measure of the drug safety, the larger the index, the safer is the drug.

Lethal dose (LD50): it is the dose that kills 50% of the experimental animals; it is also useful in finding the therapeutic dose in the early experimental studies of drug discovery. It can also be used to measure the therapeutic index a follow:

Therapeutic index = LD50/ ED50

LD 50 is the lethal dose in 50% of animals

ED50 is the effective dose in 50% of the animals

b. Agonist: any substance which has the affinity to combine with the receptors and causes receptors stimulation and pharmacological action. Example is acetylcholine which combines to muscarinic receptors and adrenaline which combines to the adrenergic receptors.
c. Partial agonist: is a drug which has affinity and some efficacy to the receptors and it does not produce maximum effect even when all the receptors are occupied and it may antagonize the action of other agonists that have a greater efficacy.
d. Antagonist: is the substance which has the affinity for the receptors but when combines with the receptors does not cause stimulation. The antagonist usually blocks or antagonizes the effect of the agonist. Example, atropine which can combine with muscarinic receptors and antagonize the effects of acetylcholine, also propranolol can combine with adrenergic receptors and antagonized the effects of adrenaline
e. Sensitivity: is the ability of a given dose of a drug to act on one system rather than the other.
f. Affinity : is the ability to combine with receptors , drugs with high affinity will displace drugs with low affinity from receptors binding
g. Potency: is a given response for certain receptor occupation, the more potent drug will give similar response at lower doses than the less potent drug, this usually determines the dose of the drug

h. Efficacy: is the maximum response to drug, this means no further increase in response occurs when we increase the dose. Drugs can have high efficacy as furosemide or low efficacy as spironolactone

i. Competitive antagonism : when two drugs compete on the same receptor site, it occurs between two drugs of similar chemical structure and usually occurs between the agonist and its antagonist on the same receptor site, example atropine can compete with acetylcholine on the muscarinic receptors. The antagonist causes parallel shift to the right of the dose response curve (i.e. you need higher dose to produce the same effect).

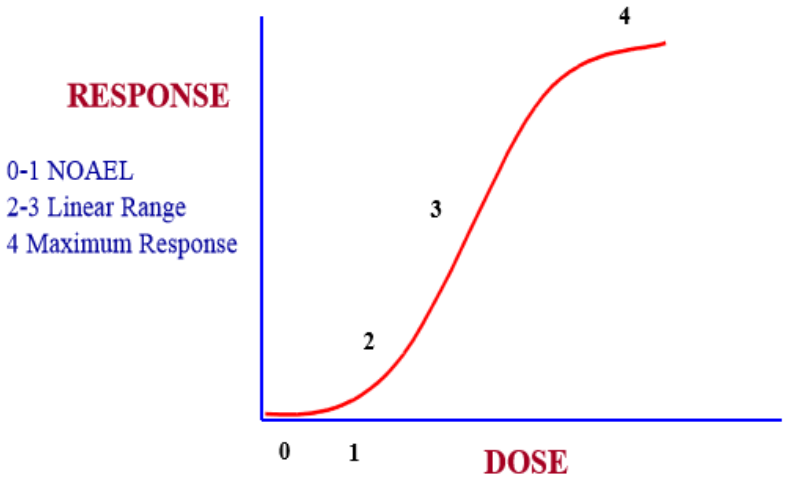
j. Physiological antagonism: Occurs when two drugs antagonize the effect of each other, but they act on two different receptors (the drugs have opposing pharmacological actions). Example is histamine which acts on histaminic receptors and causes vasodilatation, while adrenaline acts on adrenergic receptors and causes vasoconstriction , so adrenaline is a physiological antagonist to histamine and it is useful in anaphylactic reactions

Factors modifying drug response:

1. Age: various physiological changes with age that might affect the pharmacokinetics or pharmacodynamics of drugs include body fat contents, volume of distribution, hepatic blood flow, glomerular filtration rate and changes in homeostatic mechanisms.
2. Body weight: as this affects the body fluids and fat, which may change the drug concentration in the body.
3. Gender: generally lower doses for females also note hormonal, changes, menstruation, pregnancy and lactation. This can also modify the adverse effects of the drugs.

4. Racial factors Negros, Asians and Caucasians, may show different response to the same drug.
5. Genetic factors: as variation in cytochrome P450 enzymes will alter the rate of drug metabolism, also genetic deficiency of G6PD enzyme will lead to hemolysis of the red blood cell by some drugs as primaquine.
6. Disease states: include hepatic and renal diseases. These can change drug metabolism rate, drug clearance from the body and the body response to drugs.
7. Drug: dose, route of administration, frequency of administration, drug interactions, tolerance and tachyphylaxis.

- No drug only produces a single specific effect
- Drug may act on the same receptors at different cells or it may act on different receptors at the same time
- Drug effects can be divided into toxic (adverse or unwanted) and (therapeutic or useful)



DOSE DETERMINES THE BIOLOGICAL RESPONSE

Dose Response curve

0-1 initially little response
2-3 the linear portion of the dose response
4 maximum responses

4. Pharmacokinetics

Pharmacokinetics is, generally, what the body does to the drug after being taken: absorption, distribution, metabolism, excretion.

Pharmacokinetic, therefore, is concerned with the time course **(the rate)** at which drug molecules cross cell membranes to enter the body (**absorption**), to **distribute** within it and to leave the body **(excretion)** as well as with the structural changes **(metabolism)** to which they are subjected

I. Absorption

Drug passage across cell membrane

Cell membranes are essentially **bilayers of lipid** molecules with islands of proteins in between. Therefore, lipid-soluble substances can diffuse readily

Water-soluble substances of small molecular size may filter through **water-filled** channels between some epithelial and endothelial cells e.g. jejunum and proximal renal tubules

Mechanisms of passage of drugs across cell membrane

1. **Passive diffusion** (the most important)

It is the natural tendency to move passively from an area of high concentration to one of low concentration**.** The rate is concentration dependent**.** Cellular energy is **not** required

Lipid or water solubility is influenced by: structural properties of the molecules **and** environmental **pH**

Drugs are classified according to their ionization in response to environmental pH

A. Those that their **ionization is dependent on the environmental pH** (unionized=lipid soluble, ionized=water soluble)

B. Those that are **unionized** whatever the environmental pH (unionized, lipid-soluble, non-polar compounds)

C. Those that are **ionized** whatever the environmental pH (ionized, water soluble, polar compounds)

A. <u>Drugs ionized according to environmental pH</u>

The extent to which a molecule has a tendency to ionize is given by the dissociation (ionization) constant, usually expressed as the **pKa** (i.e. negative logarithm of the Ka)

- **Acidic** drugs in an **acidic** environment become: **unionized,** lipid soluble, easily diffusible

- **Acidic** drugs in an **alkaline** environment become: **ionized,** water soluble, non-diffusible

pKa is the pH at which 50% of the drug is ionized i.e. when aspirin pKa is 3.5, this means that at pH 3.5, 50% of aspirin is ionized

Gut pH varies: stomach 1.5, upper intestine 6.8, lower intestine 7.6, and pH inside the body 7.4. Therefore, aspirin in stomach (acid in acid medium): **un-ionized, lipid soluble, diffuse easily** into gastric epithelial cells. Inside epithelial cells, pH is 7.4, aspirin becomes ionized, less diffusible, and localize there **(ion trapping)(this is one mechanism for aspirin-induced gastric injury)**

B. **Drugs that are unionized whatever the environmental pH**

Example: digoxin, steroids (e.g. Prednisolone), chloramphenicol

- Unaffected by environmental pH
- Lipid soluble (non-polar compounds)
- Diffuse readily across tissues (good oral absorption)

C. Drugs that are permanently ionized drugs whatever the environmental pH

- Water-soluble (polar)
- Limited capacity to cross membranes, poor GIT absorption, usually given parenterally
- Does not cross placenta; useful in pregnancy (heparin compared with warfarin)

They are either**: negatively charged** (acidic, e.g. heparin), or **Positively charged** (basic, e.g. ipratropium, tubocurarine, suxamethonium)

2. **Carrier-mediated transport**

Active transport: In active transport, drugs are capable to move against concentration gradient, require cellular energy, more rapid than diffusion, shows high degree of specificity, subjected to saturation and can be inhibited by other compounds, and are important for some drugs with structural similarity for endogenous molecules.

Examples: Levodopa across blood brain barrier and secretion of many weak organic acids and bases through renal tubules and biliary ducts e.g. penicillin, probenecid and uric acid are actively transported in renal tubules

Large molecules can, sometimes, pass from area of high concentration to an area of low concentration through the help of specialized carrier proteins without the need for energy. This type of diffusion is called **facilitated diffusion**. Facilitated diffusion can be saturated and can be inhibited by other competitive compounds e.g. glucose and amino acid transport across cell membranes, retinols.

3. **Filtration** plays a minor role in drug transfer except for glomerular filtration. It occurs through water (aqueous) channels allowing passage of water soluble substances.
4. **Endocytosis**

Endocytosis occurs through binding to specialized components on cell membranes with subsequent engulfment (infolding of the membrane) e.g.

- Large polar molecules such as peptides
- Small polar substances such as vitamin B12 and iron combine with special proteins (intrinsic factor or transferrin) and the complexes enter the cell by this mechanism.

The order of the pharmacokinetic processes

First order processes

A constant **fraction** (**proportion**, **percentage)** of the drug is processed per unit time e.g. 10**%** of the dose is metabolized per hour

Zero-order processes

A constant **amount** of the drug is processed per unit time e.g. 10**mg** of the dose is metabolized per hour

In first order kinetics:

The rate of the pharmacokinetic process of a drug (A D M E) is **directly proportional** to the amount of the drug administered or to its concentration in the blood (high at high concentration, low at low concentration).The plasma half-life (t1/2) (which is the time for any plasma concentration to fall by 50%) is **always the same** (**constant**) when different therapeutic doses are given. The majority of drugs in doses used clinically follow first order kinetics, but in overdose, their kinetic processes may get saturated

In zero-order (saturation) kinetics, the process may become easily saturated e.g. limited amount of metabolizing enzymes.

A **small** increase in the dose can result in a **steep** and disproportionate increase in plasma concentration

Examples of drugs following zero-order kinetics in **metabolism**:
Phenytoin, theophylline, ethanol and also aspirin in high therapeutic doses

Zero-order **absorption** applies to iron, also to depot formulation and to drug implants e.g. antipsychotics and sex hormones

Plasma half-life and steady state concentration

Plasma elimination half life

is the time taken for any plasma concentration to fall by half of its original value? It is constant if elimination follows first order kinetics

Half-life can be used: to determine the dosing frequency if drug effect is directly related to plasma concentration, to calculate the time taken to reach a steady state, to calculate the time for the decline in plasma concentration after dosing ceases and to calculate the clearance and volume of distribution

$$t_{1/2} = \frac{0.693 \times Vd}{Cl} = \frac{0.693}{K}$$

The steady state concentration

When a drug is given at a constant rate, the time to reach a steady state depends on the drug half-life and is practically reached after **five half-lives.**

In a steady state: The rate of administration is equal to the rate of elimination and the plasma concentration will be at a plateau

Any increase or decrease in drug dosing, the new steady state is reached after **five** half-lives.

For example; the time required to reach a steady state concentration for dobutamine (t1/2 is 2 minutes) is 10 minutes, and for digoxin (half life is 36 hours) is 7.5 days (here, a loading dose is required to reach SS state quickly).

Half-life **varies** in the population over a range of values but a single average half life is given for clarity, **examples**:

Adenosine	< 2 seconds	Paracetamol	2 hours
Dobutamine	2 minutes	Diazepam	40 hours
Benzylpenicillin	30 minutes	Piroxicam	45 hours

Plasma concentration can be measured for therapeutic purposes **(Therapeutic Drug Monitoring, TDM)** if the drug effect is related to drug concentration at receptors in the tissues

Individual Pharmacokinetic processes

Absorption

Absorption from GIT

*Small intestine is the **main site** of absorption of drugs**.**

*Stomach does not play a major role in absorbing drugs **(small surface area, rapid gastric emptying),** even with acidic drugs; the **onset** of absorption occurs in stomach, but the main part of the dose is absorbed in the small intestine.

*The colon is also capable of absorbing drugs particularly slow-release formulations (SR).

*Buccal absorption is rapid for lipid-soluble drugs; blood flow is abundant, entry into systemic circulation avoiding first pass metabolism

Enterohepatic circulation

Bile salts are conserved about 8 times a day. A number of drugs form conjugates with glucuronic acid and are excreted in bile.

Glucuronides are polar (ionized) and are not absorbed, but the parent drugs are released by being hydrolyzed by intestinal enzymes and bacteria.

Recycling helps to sustain plasma concentration and increase duration of action. **Examples**: sulindac, ethinylestradiol

Bioavailability (Systemic availability)

Systemic availability is the percentage of the administered dose that reaches the systemic circulation intact. In simple terms, bioavailability is how much of the drug dose is available to produce a biological effect

Bioavailability is useful to:

1. Determine the dose and route of administration
   e.g. propranolol i.v. 1-10mg, oral 10-320mg (because of FPM); a drug with oral bioavailability of 5% should not be given orally
2. Compare between different formulations of a drug e.g.
   sublingual GTN >90%, oral GTN <10%
3. To know the large number of factors that might increase or decrease the systemic availability of a drug and lead to failure of therapy or to toxicity

Oral bioavailability is calculated from the equation:

$$\frac{\text{AUC oral}}{\text{AUC i.v.}} \times \frac{\text{Dose i.v.}}{\text{Dose oral}} \times 100$$

AUC = Area under plasma concentration-time curve

A drug injected i.v. is 100% available to exert its biological effect

Factors affecting systemic availability

1. **Pharmacological factors**

a. **Drug properties**: e.g. instability in gastric acid such as benzylpenicillin in gastric acid

b. **Pharmaceutical factors**: type of ingredients, compression force,….affecting disintegration and dissolution of the tablets e.g. tablets containing same amount of digoxin made by different companies may produce different plasma concentrations and therefore different effects

c. **Interaction** with other substances in the gut e.g. food and drugs (such as tetracycline binding to calcium and iron)

2. **Patient characteristics**

- disease e.g. (malabsorption, hepatic dysfunction)
- GI factors e.g. motility, pH, and blood flow
- genetic factors e.g. acetylator status: fast and slow

3. **Pre-systemic (first-pass) elimination (FPM)**

It is the extent of drug metabolism which takes place after oral administration during **first passage** of the drug through the gut wall and mainly through the liver **before reaching** the systemic circulation

Examples of drugs undergoing extensive (>50%) first pass metabolism (FPM)

Hepatic: Beta blockers (e.g. propranolol, metoprolol)
Opioids (e.g. morphine, pethidine)
Antiarrhythmics (e.g. lignocaine, verapamil)
Others (e.g. GTN, imipramine)

Gut wall: Estrogens, levodopa, isoprenaline

The importance of extensive FPM

1. It is a major **source of variations** between individuals in response to drugs. A small change in first pass metabolism will have a relatively large effect on systemic availability if the drug is extensively metabolized.
2. If the FPM is over 95% e.g. lignocaine, then the **oral route is not** suitable
3. In severe **hepatic disease** e.g. cirrhosis with both impaired liver cell function and shunting of blood into systemic circulation; FPM is reduced and systemic availability is increased (i.e. exaggerated response to normal doses)

The effect of food on drug kinetics

1. Changes in gastric emptying (slower absorption of most drugs)
2. Drug chelation (tetracycline and dietary calcium; iron and tannic acid in tea and coffee)
3. Changes in drug metabolizing enzymes (induction by alcohol, charcoal grilled beef, brussel sprout)
4. Changes in splanchnic blood flow (increased after food), FPM is reduced.

Food can <u>decrease</u> bioavailability of certain drugs: **Examples**

Ampicillin **(markedly reduced)**

Erythromycins **(except erythromycin estolate)**

Rifampicin and INH (anti-Tb)

Atenolol and captopril

Food can <u>increase</u> bioavailability of certain drugs: Examples

- propranolol, metoprolol, hydralazine
- griseofulvin, nitrofurantoin, mebendazole (particularly by fatty food)
- Erythromycin estolate

II. Distribution

The extent of distribution depends on: water/lipid solubility**,** protein and tissue binding**,** ability to cross cell membrane passively or actively

The volume of distribution (Vd)

It is a theoretical **(apparent)** volume of fluid in which the drug dose appears to distribute with a concentration equal to that in plasma

$$Vd = \frac{\text{Dose}}{C_o}$$

C_o is the initial plasma concentration, i.e. at time zero

Vd is small: if the drug remains mostly in plasma e.g. warfarin which is highly protein bound (also tolbutamide, salicylates)

Vd is large: if the drug is present mainly in the tissues e.g. digoxin, pethidine, nortriptyline, and chloroquine

The significance of the Vd

The significance of protein binding

1. It is a source of drug interaction. Displacement may be important for drugs which are highly protein bound and at the same time having small Vd e.g. warfarin and NSAIDs; the free fraction of warfarin is increased leading to bleeding

2. In renal and liver failure

The free fraction of drugs may increase and therefore, increase in response or toxicity because of hypo-albuminemia and accumulation of endogenous substances that may cause displacement from protein binding sites

III. Metabolism

Only few drugs excreted unchanged

Metabolism changes drugs in two major ways:

1. **by <u>reducing lipid solubility</u> (increased elimination)**
2. **by <u>altering biological activity</u> which occurs in 3 possible ways:**

a. Conversion of pharmacological <u>active</u> to an <u>inactive</u> substances (most drugs)

b. Conversion of <u>active</u> to another <u>active</u> substance. This prolongs the duration of action

diazepam → oxazepam

codeine → morphine

amitriptyline → nortriptyline

c. Conversion of <u>inactive</u> (a pro-drug) to <u>active</u>

levodopa → dopamine

cyclophosphamide → 4-ketocyclophosphamide

sulfasalazine → 5-aminosalicylic acid

<u>Sites of metabolism</u>

<u>Organs</u>: liver (most important)

Kidney (vitamin D, insulin)

gut mucosa (isoprenaline, levodopa, estrogen and progesterone)

Gut flora (sulfasalazine, hepatic conjugates)

lung (serotonin, noradrenaline, prostaglandins,

testosterone, isoprenaline)

skin (vitamin D activation, minoxidil, and capsaicin)

<u>Intracellular sites</u>

microsomal (mostly), mitochondria, cytoplasm, plasma

<u>Drug metabolism can occur in two phases:</u>

Phase I: The most important reaction is oxidation by mixed-function oxidases in the microsomes (the final component of these oxidases is cytochrome P450; mixed means for aliphatic and aromatic)

Phase I metabolism may occur in:

a) **the endoplasmic reticulum** (microsomal)

b) **cytoplasm**: xanthine oxidase, ethanol metabolism

c) **mitochondria**: monoamine oxidase

d) **plasma**: pseudocholinesterase, histaminase

N.B. Not all drugs broken down by enzymes e.g. melphalan which undergoes spontaneous hydroxylation to inactive metabolites

Phase II metabolism

involves union of the drug with one of the several polar (water-soluble) endogenous molecules forming water soluble conjugates readily eliminated by kidney or bile e.g. glucuronides, sulfate and others

Phase II metabolism almost invariably terminates biological activity

Examples

Glucuronide conjugation: salicylates, paracetamol, morphine

Sulfate conjugation: paracetamol, estrogen, steroids.

Acetylation e.g. INH, hydralazine (N-acetyltransferase)

Glutathione conjugation e.g. halothane, paracetamol overdose.

Most drugs undergo both phase I and II reaction; few have no major conjugates e.g. warfarin

Enzyme induction

Enzyme induction refers to the increase in enzyme amount and activity as a result of exposure to certain chemicals.

It is accompanied by hypertrophy of liver cell endoplasmic reticulum which contains most drug metabolizing enzymes.

Non-microsomal enzymes are not inducible

Examples of enzyme inducers: barbiturates, rifampicin, phenytoin, carbamazepine, griseofulvin, smoking, chronic (not acute) alcohol ingestion

The importance of enzyme induction

1. **It can be responsible for clinically important interactions**

   Examples

   a. **contraceptive failure** if potent inducers are taken at the same time
   b. **increased breakdown of vitamin D** resulting in osteomalacia and hypocalcemia; and also in megaloblastic anemia due to folate deficiency
   c. **failure of anticoagulant therapy** due to reduction of warfarin level.

2.Tolerance to certain drugs may occur e.g. with antiepileptic drugs which can induce their own metabolism

3. **Drug toxicity** may be more likely e.g. in paracetamol overdose and in patients on rifampicin or INH (hepatotoxicity)
4. **Enzyme inducers can alter liver function tests.** The level of serum bilirubin helps to distinguish the effect of enzyme induction from that of liver disease
5. **Enzyme induction can be used as a therapeutic mean e.g.** phenobarbitone can reduce severe hyperbilirubinemia in neonates by stimulation of fetal hepatic glucuronyl transferase

Enzyme inhibition

Enzyme inhibition is an important mechanism for drug-drug interaction and can lead to drug accumulation and toxicity particularly with drugs of low therapeutic index

A. **General non-specific inhibition of microsomal enzymes e.g.** cimetidine (inhibits metabolism of warfarin, diazepam, propranolol)

Other examples: sodium valproate, chloramphenicol, INH, single large dose of ethanol

B. **Inhibition of specific enzymes could be a mechanism for therapeutic action of drugs**

e.g. captopril inhibits ACE

aspirin inhibits cyclooxygenase

selegiline inhibits MAO(B)

allopurinol inhibits xanthine oxidase

Elimination

<u>Drugs can be eliminated by the following mechanisms</u>:

1. **Metabolism**
2. **Storage** e.g. highly lipid soluble drugs in fat, heavy metals in bone, phenothiazines and chloroquine in melanin-containing tissues
3. **Excretion**

IV. <u>Excretion</u>

Renal excretion: is the most important route of excretion if the drug is water-soluble and of low molecular weight

<u>Three mechanisms for excretion</u>

a. **Glomerular filtration**

- binding to plasma proteins slows the filtration rate of drugs

b. **Active tubular secretion**

- requires energy
- shows competition and saturation
- occurs in the proximal tubules

There are two active transport systems:

For **weak acids** e.g. penicillin, probenecid, phenobarbitone, aspirin

For **weak bases** e.g. amphetamine, imipramine, chloroquine

c. Tubular reabsorption

- may be active or passive
- the passive is controlled by the pH of the tubular fluid and pKa of the drug
- acids are best eliminated in alkaline urine and bases best in acid urine

Drug clearance: is the volume of the body compartments from which the drug is removed in unit time. Total body clearance of the drug is the sum of the clearances by all routes of elimination (usually hepatic and renal)

Elimination in milk

Only free (unbound) drug can be excreted in milk according to pH, pKa, and lipid-solubility

Milk pH is toward acidic side and, therefore, basic drugs ionize and may accumulate in milk. Examples of drugs contraindicated during breast feeding: chloramphenicol, anticancer drugs, and repeated doses of ergot alkaloids

Pulmonary elimination

Important for volatile anesthetics and for alcohol (from medico legal aspect)from blood to gut lumen

Fecal elimination

Either the drug is not absorbed

Passive diffusion

Biliary elimination

5. Pharmacogenetics

Learning objectives

1. Definition of pharmacogenetics
2. Examples of genetic polymorphism affecting pharmacokinetic & pharmacodynamic aspects of drugs
3. Slow and fast acetylation
4. G6PD-deficiency and drugs that cause hemolysis in G6PD deficient individuals

Human beings are 99.9% genetically identical. The remaining 0.1% will determine our reactions to environment including drugs.

Individuals in a population respond to a fixed dose of a drug as follows:

A) Continuous variation

Some will show less than usual response, most will show the usual response and some will show more than the usual response, this is presented graphically as a normal or Guassian (bell shaped) distribution curve

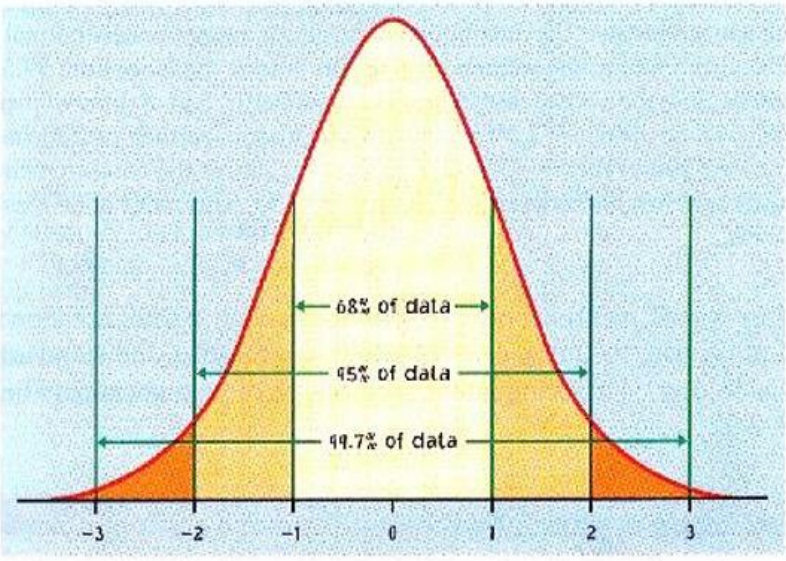


Figure 1.20 *The 68–95–99.7 rule for normal distributions.*

Factors affecting this curve are:

1. Genetic factors (multiple genes)

2. Environmental factors including race, sex, diet, weight, environmental & body temperature, circadian rhythm, pharmacokinetics and receptor density.

Note no single factor has a prominent effect.

B) Discontinuous variation (less common)

Occurs when response to a drug is controlled by a single gene (genetic polymorphism) e.g. slow and fast acetylators of INH

Pharmacogenetics

Is the study of genetically determined variation in response to drugs.

Single genes encode for particular enzymes and variant alleles produce enzymes of differing metabolic capacity that induce increased, decreased and bizarre (idiosyncratic) responses to drugs i.e. pharmacogenetic polymorphism.

Heritable conditions affecting metabolism

A. Acetylation

Is an important route of metabolism for many drugs that possess an amide ($-NH_2$) group.

Most individuals are either rapid or slow acetylators but the proportion varies greatly between races e.g. 90% of Japanese are rapid acetylators, 50% or less of Western populations are rapid acetylators

Examples of drugs that undergo acetylation:

1. INH is a drug used in TB , it is inactivated by conjugation with an acetyl group and the rate of the reaction is bimodally distributed.

In slow acetylators the patient will develop peripheral neuropathy with numbness and tingling of the hands and feet. INH is a structural analogue to pyridoxine and facilitates its excretion, so pyridoxine deficiency occurs more in slow acetylators, therefore it should be added to anti TB regimen.

In rapid acetylators, it causes acute hepatocellular necrosis because they more readily form hepatotoxic metabolite (acetyl hydrazine).

2. Hydralazine & procainamide

Cause antinuclear Abs in plasma of slow acetylators and some proceed to SLE.

3. Sulfasalazine causes adverse effects more commonly in slow acetylators because of the sulfapyridine component (which is inactivated by acetylation) causing red cell damage and mild haemolysis.

4. Dapsone causes red cell haemolysis in slow acetylators

B. Pseudocholinesterase deficiency (suxamethonium sensitivity)

Plasma pseudocholinesterase is responsible for termination of activity of suxamethonium (neuromuscular blocking agent). Affected individuals form so little plasma pseudocholinesterase that the metabolism of suxamethonium is seriously reduced.

So the patient fails to breathe spontaneously after surgical anesthesia and requires assisted ventilation for hours.

Heritable conditions affecting drug response

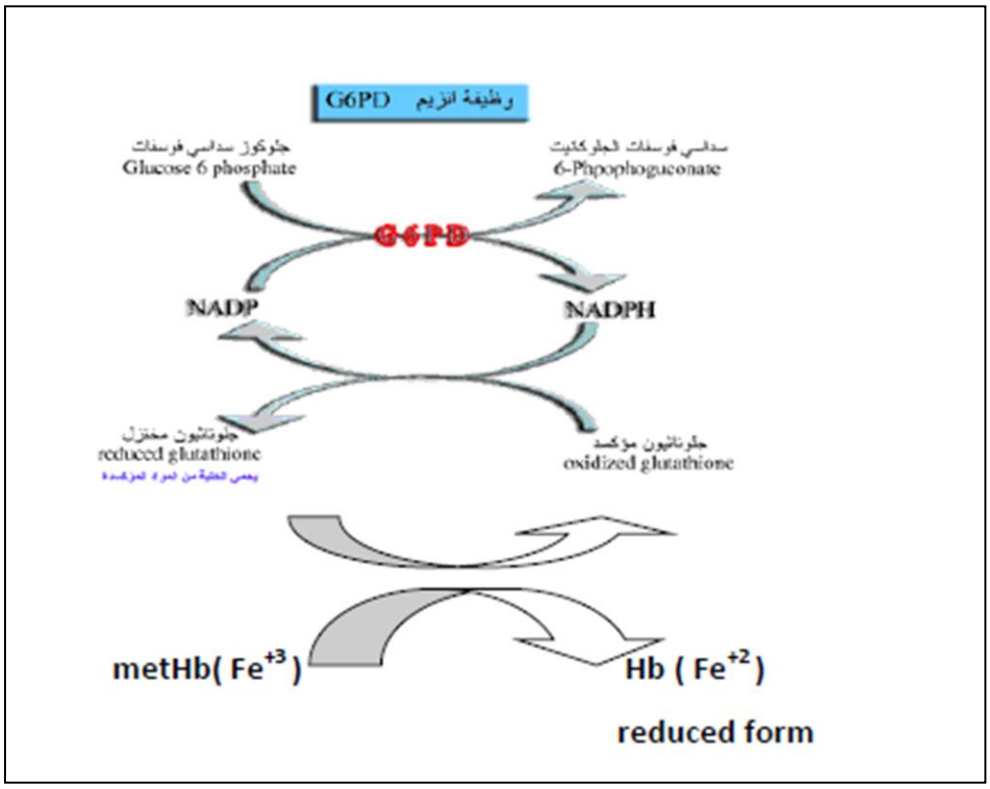
Glucose-6-phosphate dehydrogenase (G6PD)deficiency

G6PD activity is important to the integrity of the red blood cell through a chain of reactions:

1. It is an important source of reduced nicotinamide-adenine dineucleotide phosphate (NADPH) which maintains erythrocyte glutathione in a reduced form.

2.Reduced glutathione is necessary to keep Hb in reduced (Fe^{+2}), rather (Fe^{+3}) oxidized (metHb) form which is useless for O_2 carriage.

3.Buildup of metHb in erythtocytes impairs the function of sulfhydryl group especially those associated with the stability of the cell membrane.



G6PD deficiency is determined by sex-linked gene carried on x-chromosome. This condition is common in African, Mediterranean, Middle Eastern and South Asian races.

Haemolysis: occurs in G6PD-deficient subjects if they are exposed to certain oxidant substances which include:

1. Drugs are of 2 types:

a. Those that carry definite risk of haemolysis including: dapsone, methylene blue, niridazole, nitrofurantoin, primaquine, pamaquine, quinolone antimicrobials, some sulfonamides.

b. Those that carry possible risk of haemolysis including: aspirin(dose>1g/day), menadione, probenecid, quinidine, chloroquine, quinine, chloramphenicol.

2. Chemical substances including:

Nitrates, anilines, naphthalenes (found in moth balls).

3. Food: raw broad beans esp.in children or their pollen (*vicia faba*) so it is called (favism).

Note

*Hemolysis occurs 2-3 days after using the drug and is self-limiting

*only older cells with least enzymes are affected

6. Autonomic nervous system

Learning objectives

1.Few points about the physiology of autonomic nervous system

2. Acetylcholine as a transmitter of parasympathetic system, its synthesis and release

3.Classification of cholinergic receptors, their location and the pharmacological actions induced by their stimulation

4.Classification of cholinergic drugs

5.Organophosphorus poisoning

6. Classification of anti-cholinergic drugs

7.Atropine as a prototype of anti-muscarinic drugs

Autonomic nervous system

It is an independent system i.e. its activities are not under direct control, it includes:

1.Sympathetic(thoracolumbar) division

2.Parasympathetic(craniosacral) division

Both divisions originate in nuclei within CNS and give rise to preganglionic efferent fibers that exit from the brain stem or spinal cord and terminate in motor ganglia.

*Almost all efferent fibers leaving CNS are cholinergic.

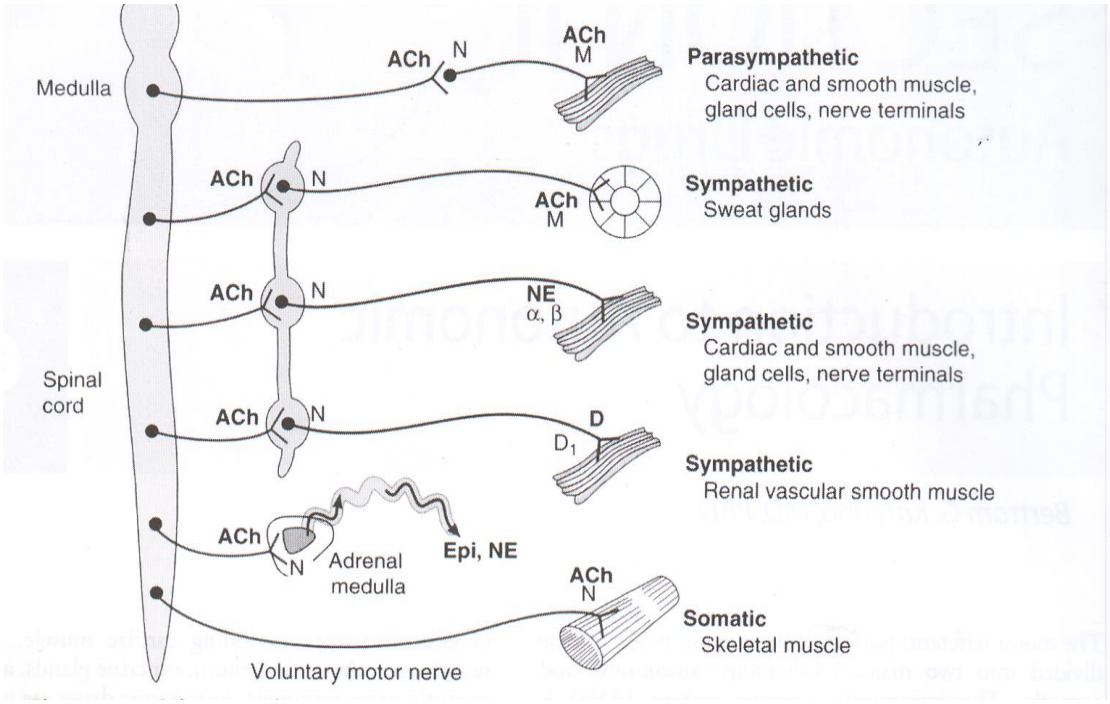
*All preganglionic efferent autonomic fibers and the somatic (non-autonomic) motor fibers to skeletal muscles are cholinergic.

*Most parasympathetic postganglionic & few sympathetic postganglionic fibers are cholinergic.

*Most postganglionic sympathetic fibers release noradrenaline so are adrenergic.

*Dopamine is a very important transmitter in CNS & there is evidence that it may be released by some peripheral sympathetic fibers.

*Adrenal medullary cells (an embryological analogue to postganglionic sympathetic neurons) release a mixture of adrenaline &nor-adrenaline.



PARASYMPATHETIC SYSTEM

Acetylcholine (Ach) is a wide spread chemo transmitter in the body mediating a broad range of physiological effects.

Synthesis & release

Ach is synthesized in the cytoplasm from

Acetyl CoA + Choline $\xrightarrow{\text{ChAT (choline acetyl transferase)}}$ **Ach**

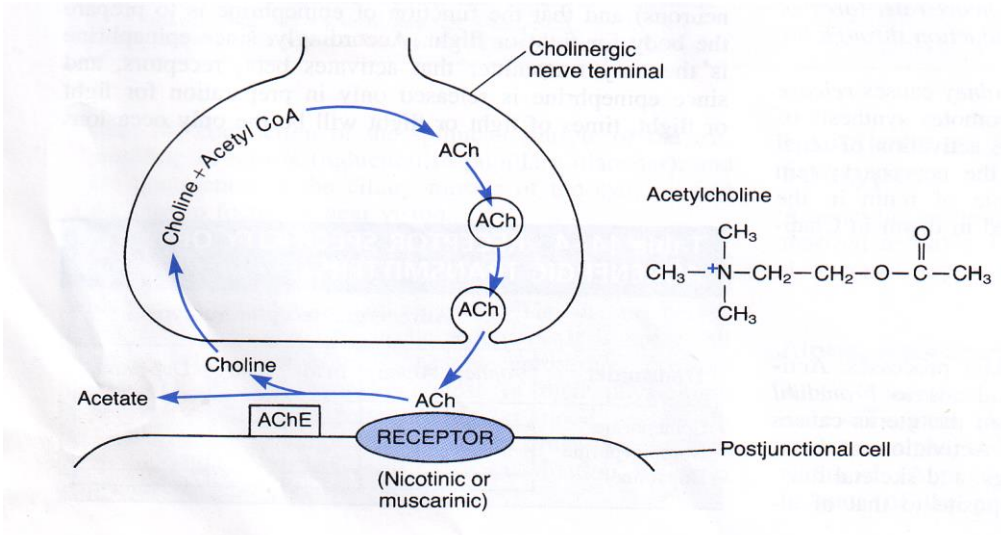
Once synthesized, Ach is stored in vesicles & then released in response to action potential.

*After release from presynaptic terminal:

1.Ach binds to & activates receptors located in postjunctional cells (cholinoceptors).

2.Ach is destroyed by cholinesterase which splits Ach to choline & acetate (neither of each has significant transmitter effect)

*choline is taken up into the cholinergic nerve terminal.



*Most cholinergic synapses are richly supplied with cholinesterase so half-life of Ach is very short (seconds).

*Cholinesterase enzyme is of 2 types:

1.True- found at cholinergic nerve endings & in RBCs

2.False(pseudo cholinesterase)-has a lower specificity for Ach & is found in blood plasma, liver & many other tissues.

Mechanism of action

There are 2 distinct classes of receptors for Ach defined on the basis of their activation by alkaloids:

1.Muscarinicreceptors(activated by muscarine) which are of 5 subtypes:

a.M_1-in gastric parietal cells

b.M_2-in heart, nerves, smooth muscles

c.M_3-in exocrine glands, smooth muscles and bladder

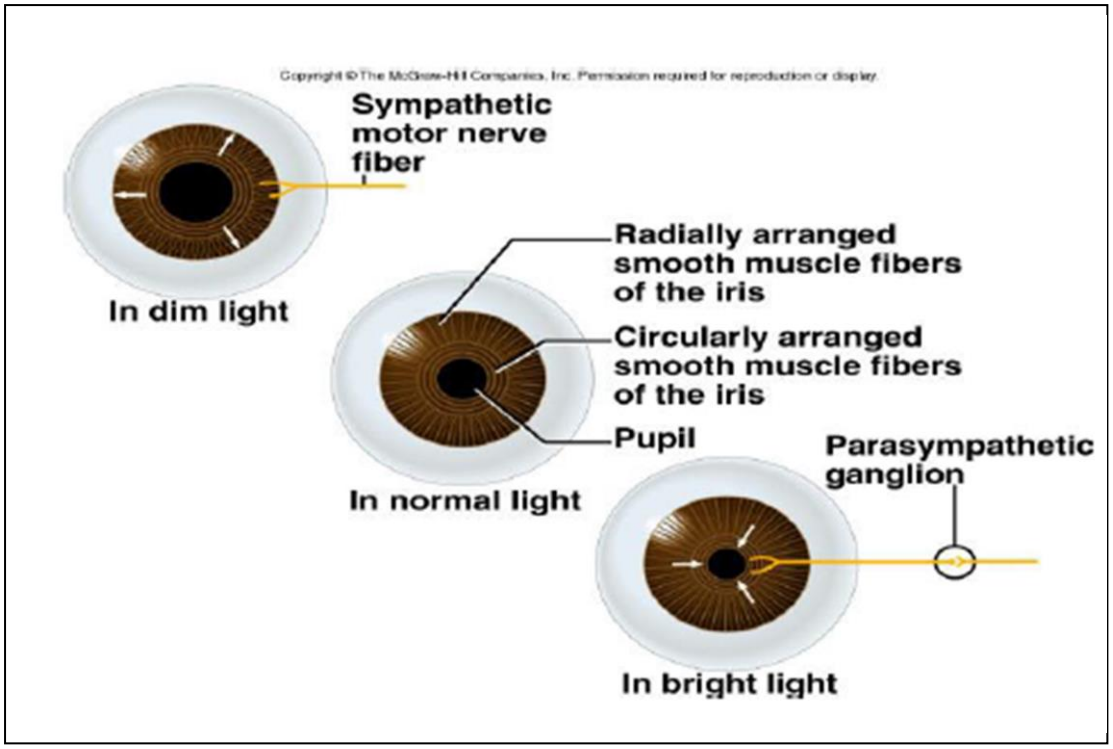
d.M_4 &M_5-in CNS

2.Nicotinic receptors (activated by nicotine) - are found at neuromuscular junctions and their stimulation causes muscle fasciculation.

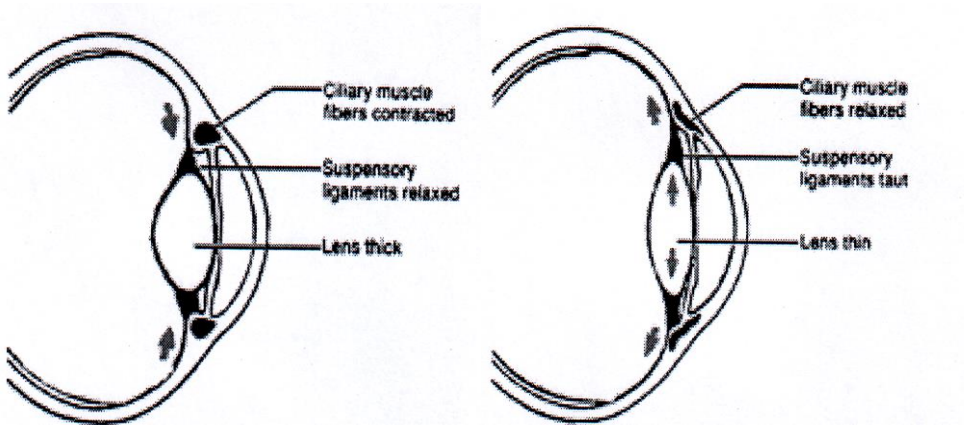
Muscarinic receptors are found in the following sites:

A. Smooth muscles

a.Eye- stimulation of the receptors causes miosis due to contraction of circular muscle of the iris (constrictor pupillae).



The eye is also accommodated for near vision due to contraction of ciliary muscle

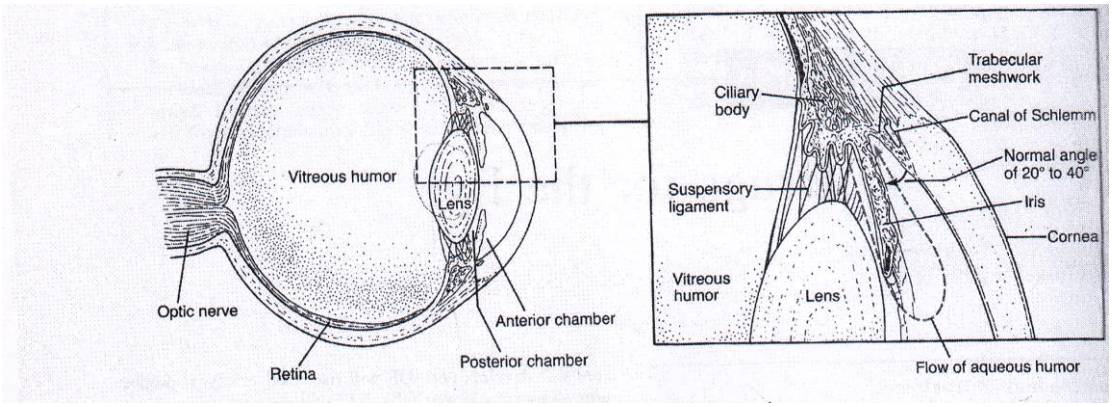


Intra-ocular pressure also falls by:

1. Miosis- the iris is pulled away from the angle of the anterior chamber

2.Contraction of ciliary muscle, the trabecular meshwork, on the base of the ciliary muscle, is opened)

Both these effects facilitate aqueous humor flow into canal of schlemm.



b.Bronchi-bronchoconstriction & mucosal hyper secretion

c.Gastrointestinal tract (GIT)- stimulation causes:

* increased motor & secretory activity of the gut and may cause colicky pain.

*increased exocrine secretions mainly of salivary & gastric glands while pancreas & small intestinal glands are less stimulated.

*Relaxation of sphincters-anal sphincter(causes defecation)

-esophageal sphincter(causes regurgitation)

d. Genitourinary tract (GUT)

Contraction of detrusor muscle, relaxation of trigone & sphincter's muscles which promote micturition.

B. Exocrine glands- increased secretions mainly of salivary, lachrymal, bronchial & sweat glands.

Sweat glands are cholinergic, although anatomically are part of sympathetic system, axillary sweat glands are adrenergic.

C. Cardiovascular system (CVS)-(effects are through M_2 receptors)

Stimulation causes bradycardia and AV block. It also causes vasodilatation and lowering of blood pressure by indirect mechanism through releasing of nitric oxide.

Note

Both muscarinic & nicotinic receptors are found in the central nervous system (CNS) and causing stimulation followed by depression.

Cholinergic drugs (Parasympathomimetic drugs) include:

1.Directly acting (act directly at cholinergic receptors) including:

a. cholinesters

b. alkaloids

2.Indirectly acting drugs (cholinesterase inhibitors- influence cholinergic receptors indirectly by preventing the breakdown of Ach including:

a. reversible anti-cholinesterases

b. irreversible anti-cholinesterases

I. Directly acting drugs

A. Cholinesters

1. Acetyl choline– is a substance with huge variety of effects on both muscarinic & nicotinic receptors and is rapidly destroyed in the body, so is unlikely to be useful when given systemically.

2. Carbachol & Bethanecol

Are not destroyed by cholinesterase, their actions are more pronounced on the bladder & GIT, so are used to stimulate these organs e.g. after surgery.

B. Alkaloids

a. Nicotine- is absorbed through mucous membranes. Its $t_{1/2}$ is 2h, is metabolized by CYP450.

*In large doses- acts at autonomic ganglia &voluntary neuromuscular junction causing paralysis. CNS is first stimulated (causing vomiting, tremor, convulsion) & followed by depression.

***clinical use-** is a social drug used as an adjunct to stopping its own abuse as tobacco.

b. Muscarine- is of no therapeutic use.

*it has a role in discovery of cholinergic receptor subtypes

*has a toxicological significance because of its presence in certain poisonous mushrooms.

c. Pilocarpine

Is a direct acting muscarinic agonist, also stimulates then depress CNS

Clinical uses

1.Glaucoma , it decreases IOP by miosis & contraction of ciliary muscle

2.is used orally for treatment of xerostomoia (dry mouth) following irradiation of head & neck tumors

Adverse effects -decreased visual acuity, local irritation& eye pain, rarely is absorbed in amounts sufficient to cause systemic effects (bradycardia, bronchospasm, hypotension, urinary urgency, diarrhea, hyper salivation & sweating)

*It should be cautiously used in patients with bronchial asthma or bradycardia

*Its systemic toxicity is reversed by atropine

*It is available as a solution(eye drops) 0.25-10%, a gel(4%)

II. Indirectly acting drugs

They are cholinesterase inhibitors (Anticholinesterases)

that prevent degradation of Ach by cholinesterase, are of 2 types:

1.Reversible- produce effects of moderate duration

2.Irreversible- produce long lasting effects

A. Reversible inhibitors

a. Neostigmine ($t_{1/2}$=2h)

Is a synthetic reversible anticholinesterse whose action is more prominent on neuromuscular junction.

It contains quaternary nitrogen atom, so it is poorly absorbed after oral administration and it cannot readily cross membranes including of GIT, BBB & placenta.

Pharmacological effects- intensifies transmission at all junctions where Ach is a transmitter

Pharmacokinetics can be administered orally, s.c, i.m, i.v, duration of action is 2-4 h, cannot cross BBB, eliminated by enzymatic degradation.

Is used in myasthenia gravis

b. Physostigmine is similar to neostigmine, but is not quaternary ammonium compound, so can readily cross membranes like BBB.

Uses

1.is drug of choice in treatment of atropine poisoning because it
can cross BBB & reverse muscarinic blockade in CNS

2.glaucoma

c. Pyridostigmine is similar to neostigmine, but has less powerful action that is slower in onset & slightly longer in duration.

It is **used in** myasthenia gravis.

d. Edrophonium is structurally related to neostigmine but its action is brief.

Uses:

a. diagnosis of myasthenia gravis

b. to differentiate between myasthenic crisis (is improved) and
cholinergic crisis (is aggravated)

***A more recent use of anticholinesterase drugs is to improve cognitive function in patients with Alzheimer's disease like: Donepezil, galantamine, rivastigmine.**

Myasthenia gravis

Is an autoimmune disease where there is impairment of synaptic transmission at NMJ, 85% of patients have raised titer of auto Abs to the nicotinic Ach receptors. These Abs accelerate receptor turnover, shortening their life time in skeletal muscle membrane from 7 days to 1 day in myasthenic patients.

Clinical features: diplopia, fatigue, ptosis, difficulty in speaking & swallowing.

Diagnosis

1. Edrophonium i.v, will dramatically & transiently relieve myasthenic muscular weakness.
2. Measurement of Ach receptor Abs titer to confirm diagnosis.

Treatment

Anticholinesterase drugs, pyridostigmine is preferred because its action is smoother than neostigmine.

Neostigmine has more rapid onset of action so has an advantage to be given in the morning to get the patient mobile.

*These drugs are given orally, but can be given parenterally if there is difficulty of swallowing.

B. Irreversible cholinesterase inhibitors

Are highly toxic, employed primarily as insecticides. They are also developed, to be used in war called as nerve gases but they are volatile liquids.

They are organophosphate cholinesterase inhibitors because they contain an atom of phosphorus. They are highly lipid soluble so are readily absorbed from all routes of administration like skin, GIT & inhalation. Once they are absorbed, they have readily access to all tissues & organs including CNS.

Mechanism of action

They bind irreversibly to the active center of cholinesterase so preventing the enzyme from hydrolyzing Ach. Because of irreversible binding, effects persist until new molecules of cholinesterase are synthesized.

Typical features of acute poisoning

1.GIT-salivation, vomiting, abdominal cramps, diarrhea, and involuntary defecation

2.Respiratory system-bronco-constriction, increased bronchial secretions, cough, wheezing & dyspnea

3.CVS-bradycardia

4.GUT-involuntary micturition

5.Skin- sweating

6.Skeletal system- muscle weakness & twitching

7.CNS- miosis, anxiety, headache, convulsions, respiratory failure

***death is due to respiratory failure (action in CNS causing respiratory muscle paralysis) & due to excessive bronchial secretions & bronco-constriction.**

Treatment

1.contaminated clothes should be removed & skin washed

2.atropine 2mg i.m or i.v & repeated every 15-60 min until dryness of mouth & heart rate exceeding 70 beats/min which indicates adequate effect

3.mechanical ventilation

4.diazepam for convulsions

5.atropine eye drops to relieve headache caused by miosis

6.enzyme reactivation- pralidoxime reverses poisoning by dissociating organophosphate inhibitors from the active center of cholinesterase. It is given by a slow i.v injection over 5-10 min.

*Its efficacy is greatest if administered within the first 12 hr of poisoning, if significant reactivation occurs, muscle power improves within 30 min.

*It cannot cross BBB, so cannot reverse cholinesterase inhibition in CNS.

Anticholinergic drugs

They are divided into:

1. Antimuscarinic drugs(atropine related drugs) act principally at postganglionic cholinergic (parasympathetic) nerve endings

2.Antinicotinic drugs: a)ganglion-blocking drugs

b)neuromuscular blocking drugs

I. Antimuscarinic drugs (parasympatholytic drugs)

A. Atropine (belladonna alkaloid)

Is the prototype of this group, is an alkaloid from the deadly night shade *Atropa belladonna*.

Mechanism of action

It competitively & selectively blocks muscarinic receptors at therapeutic doses, but in sufficiently high doses, it produces some blockade of nicotinic receptors as well.

Pharmacological effects

a. Exocrine glands-all secretions, except milk, are diminished. Dry mouth & dry eye are common. Gastric acid secretion is reduced as well as the volume of gastric secretion, so PH is little altered. Sweating is inhibited, bronchial secretions are reduced & become viscid as removal of secretions by cough & ciliary action is rendered less effective.

b. Smooth muscles: are relaxed, decreased tone & peristalsis in GIT, bronchodilatation, decreased micturition & urinary retention may be induced especially in preexisting prostatic enlargement.

c. Ocular effects mydriasis with increased IOP, accommodation for far vision due to paralysis of ciliary muscle (cycloplegia).

d. CVS: reduces vagal tone, so causes tachycardia & enhanced conduction in bundle of His, has no significant effect on peripheral blood vessels in therapeutic doses but in overdose causes marked vasodilatation.

e. CNS: causes mild CNS stimulation at therapeutic doses, in toxic doses it causes hallucination & delirium, extremely high doses result in coma, respiratory arrest & death.

*atropine is readily absorbed from GIT, can be given orally, topically & injection.

Clinical uses

1.preanesthetic medication

2.in ophthalmology

3.bradycardia following myocardial infarction

4.cholinergic poisoning

Adverse effects: dry mouth, blurred vision & photophobia, increased IOP, urinary hesitancy or urinary retention, constipation, anhidrosis (deficiency or absence of sweat) & hyperthermia, thickening & drying of bronchial secretions resulting in bronchial plugging.

Contraindications

1.Glaucoma

2.Prostatic hypertrophy

3.Patients with tachycardia

4.Intestinal atony

Atropine poisoning

Is characterized by dry mouth, blurring of vision, photophobia, hyperthermia, CNS effects(hallucination & delirium), and hot dry & flushed skin.

*death results from respiratory depression secondary to blockade of cholinergic receptors in brain.

Treatment

1.minimizing absorption- by syrup of ipecac to induce vomiting, & activated charcoal to adsorb the poison within intestine

2.Antidote- physostigmine, because it crosses BBB.

B. Hyoscine (scopolamine)

Is structurally close relative to atropine.

*The main difference: a. is CNS depressant, causes confusion esp. in elderly

b. mydriasis is briefer than atropine

c. suppresses emesis& motion sickness

C. Hyoscine butylbromide (Buscopan)

Also blocks autonomic ganglia. If injected, it is effective relaxant of smooth muscles including cardia, pyloric antral region & colon. So is useful in colic & endoscopy.

D. Homatropine

Is used as eye drops , its action is shorter than atropine, so less likely to cause serious increased IOP, the effect wears off in a day or two.

E. Tropicamide (Mydriacyl) & Cyclopentolate (Mydrilate)

Are used as eye drops for mydriasis & cycloplegia, are quicker & shorter acting than homatropine, produce mydriasis within 10-20min & duration of action is 4-12h.

F. Ipratropium (Atrovent)

Is used as an inhaled bronchodilator for acute bronchial asthma & chronic obstructive pulmonary disease.

G. Flavoxate (Urispas) & Oxybutynin (Cystrin)

Is used for urinary frequency, tenesmus, and urgency incontinence because it increases bladder capacity & reduces unstable detrusor contractions.

H. Propantheline (Pro-Banthine)

Is used as smooth muscle relaxant e.g. in irritable bowel syndrome & diagnostic procedures.

I. Benzhexol & Orphenadrine used in parkinsonism.

J. Promethazine is used as an antiemetic.

II. Ganglion-blocking drugs

They have limited applications because they lack selectivity, so their only use is to lower blood pressure& only in special circumstances.

E.g.

Mecamylamine (Inversine): is the only available drug in USA

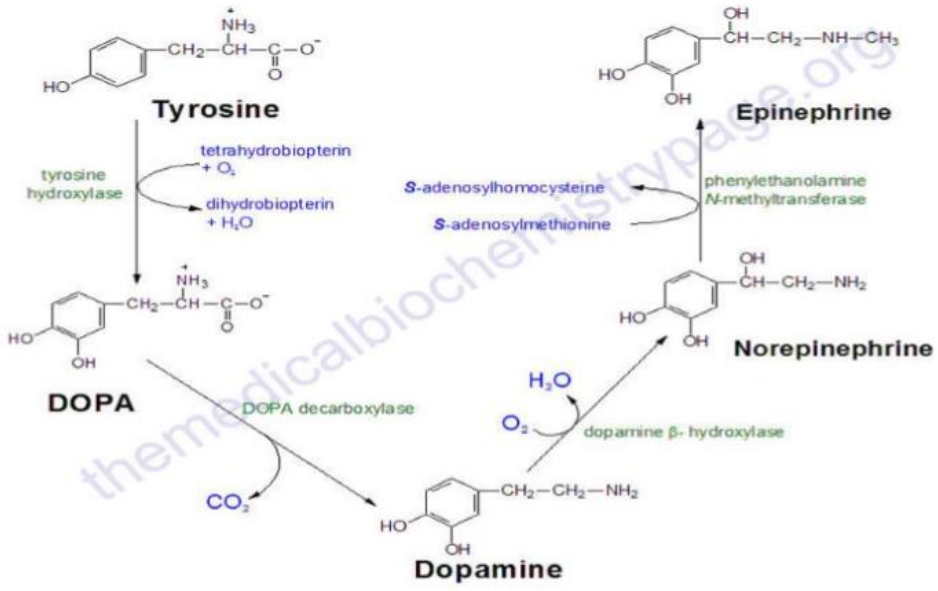
7. Sympathetic (Adrenergic) system

Learning objectives

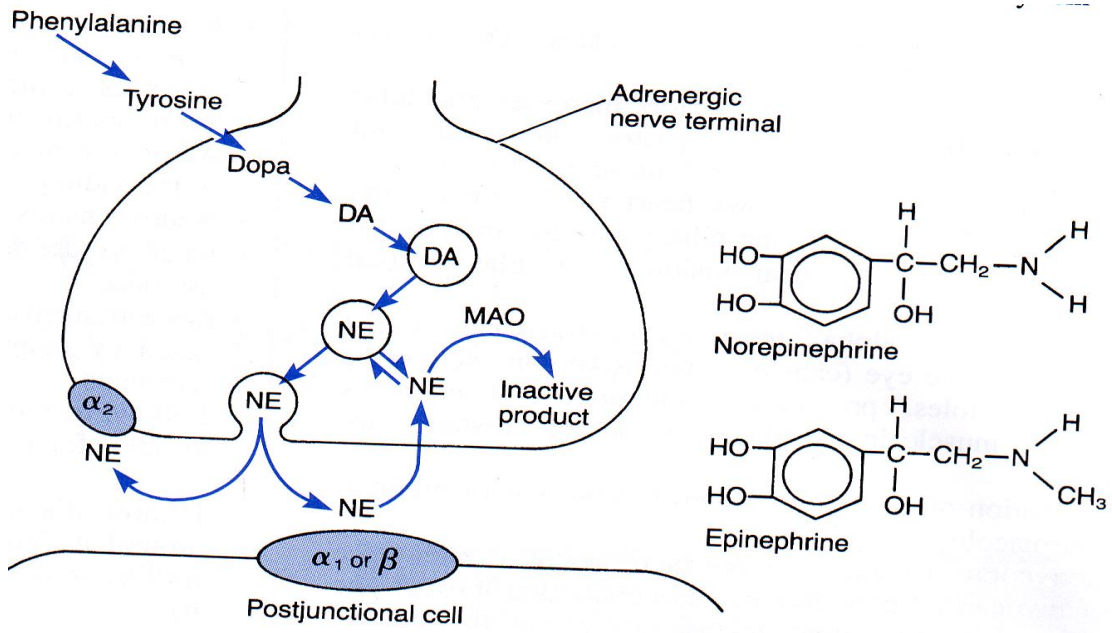
1. Synthesis and release of the transmitters
2. Fate of released noradrenaline
3. Classification of adrenoceptors
4. The pharmacological actions induced by adrenoceptors stimulation
5. Classification of sympathomimetic drugs
6. Differences between catecholamines and non-catecholamines
7. Difference between selective and non-selective α-blockers
8. Differences between selective and non-selective β- blockers
9. Pharmacological details of sympathomimetic and sympatholytic drugs
10. Examples of adrenergic neuron blocking drugs and centrally acting α2 agonists.

The transmitters are norepinephrine (noradrenaline), epinephrine (adrenaline) & dopamine.

Synthesis & release



Noradrenaline (NA) is converted enzymatically to adrenaline (A) in adrenal medulla.



After release of NA, the fate is:

1. Re-uptake into nerve terminals (following this re-uptake, either it is taken to vesicles for reuse, or degraded by monoamine oxidase, MAO)
2. Binding to receptors
3. Metabolism by extra neuronal MAO (mono amine oxidase) & COMT (catechol-O-methyl transferase) enzymes.

Adrenergic receptors

I. Alpha-receptors are of two subtypes:

a. Alpha 1 (α1)- their stimulation in:

1. Eye- causes contraction of radial muscle of iris leading to mydriasis

2. Blood vessels- causes VC (present in veins & arterioles in many capillary beds)

3. Sexual apparatus in male- causes ejaculation

4. Smooth muscle of bladder neck & prostatic capsule- causes contraction

5. Uterus- causes contraction of pregnant uterus

6. Skin- causes sweating, pilomotor action

7. Blood- causes platelet aggregation

8. Intestinal smooth muscle- causes relaxation

9. Have metabolic effects causing hyperkalemia

b. Alpha 2 (α2)- are found in nerve terminals & not on the organs innervated by ANS, so they are called presynaptic or prejunctional auto-receptors.

Their function is to regulate transmitter release, so NA binds to α2 receptors causing suppression of further NA release (mediate negative feedback inhibition of NA release).

*α2 receptors are also found in the CNS, which are therapeutically important.

II. Beta-receptors: are of two subtypes:

a. Beta 1 (β1)- are found in:

1. Heart: their stimulation increases heart rate (chronotropic effect), increases conductivity through AV node, increases automaticity (AV node & muscle), increases contractility of myocardium (inotropic effect), increases O2 consumption, decreases refractory period of all tissues.

2. kidneys: stimulation causes release of renin into blood.

3. Have metabolic effects causing lipolysis

b. Beta 2 (β2)- mediate the following pharmacological effects:

1. increase in heart rate

2. bronchodilatation

3. relaxation of pregnant uterus

4. its stimulation in skeletal muscle causes tremor

5. relaxation of arterioles

6. metabolic effects hypokalemia, hepatic glycogenolysis & lipolysis

7. bladder detrusor muscle relaxation

8. anti-inflammatory effects by inhibition of autacoids release (histamine, leukotriens) from mast cells.

9. relaxation of intestinal smooth muscles.

III. Dopamine receptors

In periphery, the only dopamine receptors of clinical significance are located in vasculature of kidneys.

*Their activation dilates renal BV so enhancing renal perfusion.

*In CNS, dopamine receptors are of great therapeutic significance

NOTE

***Adrenaline activates α & β but not dopamine receptors.**

***Noradrenaline activates α1, α2, β1 receptors but not β2 or dopamine receptors.**

***Dopamine activates α1, β1 & dopamine receptors.**

NOTE: the concept of receptor specificity is relative- at low doses, the selectivity is maximal, as dose increases the selectivity declines.

Sympathomimetics (Adrenergic agonists)

They are classified according to their mode of action:

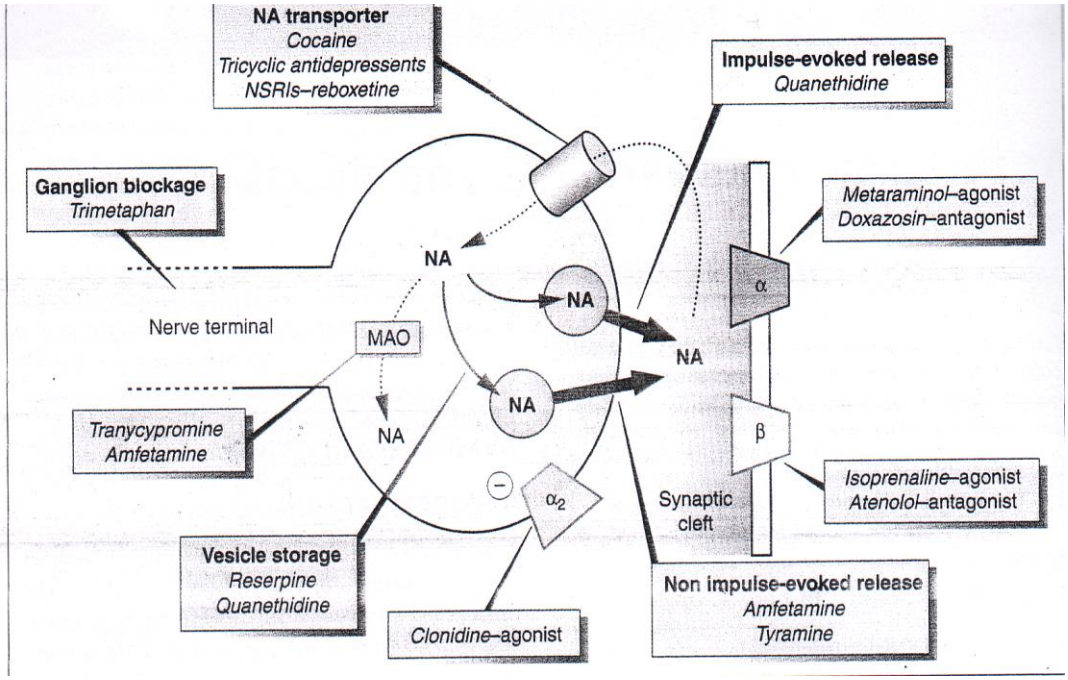
1. Directly acting adrenoceptor agonists: e.g. adrenaline, noradrenaline, dopamine, isoprenaline, and phenylephrine.

2. Indirectly acting adrenoceptor agonists-act by releasing NA from stores at nerve endings e.g. amphetamine, ephedrine.

3. By both mechanisms (1&2)-include other synthetic agents.

*There are drugs that block re-uptake of NA in adrenergic nerve terminals e.g. cocaine, tricyclic antidepressants, reboxetine (highly NA selective re-uptake inhibitor-NSRIs)

*There are drugs that destroy or deplete intracellular stores within adrenergic nerve terminals e.g. reserpine, guanethidine.



Catecholamines

Are so named because they contain **a catechol group (**benzene ring with hydroxyl group) & **an amine group,** include: **noradrenaline, adrenaline, isoprenaline, dopamine, and dobutamine.**

*They have 3 properties in common:

1. cannot be taken orally
2. have brief duration of action
3. cannot cross BBB (because they are polar)

*MAO & COMT are present in large amounts in liver & kidney, & account for most of the metabolism of injected catecholamines. MAO is also present in intestinal mucosa, in peripheral & central nerve endings.

*These enzymes are very active & quickly destroy catecholamines administered by any route (if taken orally, they will be destroyed before reaching systemic circulation); so catecholamines are ineffective when swallowed.

Non catecholamines

They do not contain a catechol group, include: **ephedrine, phenylephrine, salbutamol, terbutaline.**

*They differ from catecholamines by:

1. are not substrate for COMT & metabolized slowly by MAO
2. have longer $t_{1/2}$
3. can be given orally
4. less polar, more liability to cross BBB & produce CNS effects

I. Catecholamines

A. Adrenaline

Is a catecholamine, stimulates α1, α2, β1&β2 receptors.

Pharmacokinetics– it is administered topically, by injection, & by inhalation. It cannot be given orally because it is destroyed by MAO & COMT before reaching systemic circulation.

*It has short $t_{1/2}$ because of enzymatic inactivation

Therapeutic uses

1. Because of α1 mediated VC, it is used to:
    a) delay the absorption of local anesthetics
    b) control superficial bleeding
    c) reduce nasal congestion

d) elevate BP

2. Is used as mydriatic (sparing accommodation) & also lowers IOP

3. To overcome AV block & restore cardiac function in patients undergoing cardiac arrest

4. Bronchial asthma

5. Is treatment of choice in anaphylactic shock (because of CVS & bronchial actions & also stabilize mast cell membranes & reduce release of vasoactive autacoids)

Adverse effects

1. hypertensive crisis & cerebral hemorrhage

2. dysrhythmia- esp. in hyperthyroid patients

3. angina pectoris, esp. in patients with atherosclerosis

4. necrosis following extravasation

5. hyperglycemia in diabetic patients

Drug interactions

1. MAOI- prolongs & intensifies effect of adrenaline

2. Tricyclic antidepressants- block uptake of catecholamines into adrenergic neurons, so intensify & prolong action of adrenaline.

3. General anesthetics- like halothane, sensitize myocardium to catecholamines leading to arrhythmias

B. Noradrenaline

Is a catecholamine acts on α1, α2 & β1 receptors

Uses: 1. hypotensive state

2. cardiac arrest

3. vasodilation of septic shock

Adverse effects: peripheral gangrene, local necrosis

C. Isoprenaline (Isoproterenol)

Is a catecholamine acts on β1 & β2 receptors. Has a vigorous stimulant effect on heart.

Clinical uses

1. complete heart block
2. bronchial asthma, its use is declined because of its stimulant effect on heart
3. overdose of β blockers

Adverse effects arrhythmia, angina, and hyperglycemia in diabetic patient

D. Dopamine

*At lowest effective dose, it stimulates D1 receptors in CNS, renal & other vascular beds (dilator). Also activates presynaptic auto receptors (D2) which suppress release of NA.

*As the dose increases, it stimulates β1 receptors in heart

*it is given by i.v infusion because of short $t_{1/2}$ =2min.

Therapeutic uses

Is used in shock, a) by activating β1 receptors, it increases CO & improving tissue perfusion

b) by activating dopamine receptors in kidney, it dilates renal BV so improve renal perfusion & decreases risk of renal failure.

Adverse effects

Tachycardia, arrhythmia, angina pain, extravasation results in necrosis from localized VC

E. Dobutamine

It is useful in shock, given with dopamine

II. Non-catecholamines

A. Phenylephrine has action similar to NA but of longer duration up to several hours. Is a selective α1 agonist.

Is used 1. as a nasal decongestant

2. parenterally to elevate BP

3. as a mydriatic & briefly lowers IOP (as eye drops)

B. Ephedrine

It activates all adrenergic receptors by direct (binding to receptors) & indirect (by stimulating release of NA from adrenergic neurons) mechanisms. It is a plant alkaloid.

*in adults, it increases alertness, causes anxiety, tremor & nausea, but it may be sleepy in children.

Is used

1. orally for reversible airway obstruction
2. in nasal congestion (mucosal vasoconstrictor)
3. topically as mydriatic

Adverse effects: hypertension, arrhythmias, angina, hyperglycemia, insomnia

C. Amphetamine (Benzedrine) & Dexamphetamine (Dexedrine)

Act indirectly.

Their use is for effects on CNS in:

1. narcolepsy
2. attention deficit in children

D. Salbutamol (Ventolin)

Is a selective β2 agonist, taken orally, by inhalation & by injection, $t_{1/2}$=4h, it acts quickly by inhalation & action lasts for 4-6h

Uses

1. bronchial asthma (treatment & prevention)

2. premature uterine contraction

Adverse effects: tachycardia, hypokalemia, tremor

E. Salmeterol (Serevent)

Is a selective β2 agonist, acting longer because its lipophilic side chain anchors the drug adjacent to the receptor, which results in slow onset & longer duration of action (12-18h).

Adrenoceptor blocking drugs

These drugs occupy the adrenoceptors in competition with A & NA, whether released from stores in nerve terminals or injected.

They are classified into:

1. α-adrenoceptor blocking drugs
2. β-adrenoceptor blocking drugs

I. Alpha-adrenoceptor blocking drugs

A. Selective α1 blockers

a. Prazosin (Minipress)

It blocks postsynaptic α1& not presynaptic α2 receptors, so causes dilatation of arterioles & veins**.**

Uses

1. hypertension
2. benign prostatic hypertrophy- results from proliferation of cells in prostate gland.

*Benefits of prazosin result from reduced contraction of smooth muscle in bladder neck & prostatic capsule.

Adverse effects

1. Postural hypotension (dizziness, light headedness), about 1% of patients lose consciousness 30-60 min after receiving their first dose **(first dose effect)** as a result of severe postural hypotension.

*To minimize the first dose effect:

a. the initial dose should be small (0.5 mg)

b. warning the patient about this effect &advising him to avoid driving & other hazardous activities for 12-24h

c. administering the first dose at bedtime

2. Reflex tachycardia, inhibition of ejaculation & nasal congestion

b. Doxazosin (Cardura)

Is a selective α1 blocker, given once daily, $t_{1/2}$=8h. The first dose effect is much less marked, although it is still advisable to start patients with small dose. It has same clinical uses and adverse effects of prazosin.

B. Non-selective α-blocking drugs

a. Phentolamine

Is a non-selective competitive α adrenergic blocking drug.

*It has also direct vasodilator & cardiac inotropic actions.

Uses is given i.v for brief effect in adrenergic hypertensive crisis e.g. phaeochromocytoma or MAOI-sympathomimetic interaction.

Adverse effects: postural hypotension, reflex tachycardia, nasal congestion & inhibition of ejaculation

***It produces greater reflex tachycardia than selective blockers because it blocks α2 receptors as well.**

b. Phenoxybenzamine

Is an irreversible non-selective α adrenoceptor blocking drug, its effect may last for 2 days or longer.

*Effects subside as newly synthesized receptors replace the ones that have been irreversibly blocked.

*Its **only use** is in phaeochromocytoma

*It has the same adverse effects of phentolamine

c. Labetalol

Is α&β blocker, used parenterally in hypertensive emergencies.

II. Beta-adrenoceptor blocking drugs

Selectively block β receptors. They may be pure antagonists & some are partial agonists.

Pharmacological effects

Result from reduction of sympathetic drive including: decreased automaticity (heart rate), decreased myocardial contractility, decreased renin secretion. Then CO & overall cardiac O_2 consumption falls.

*The effects are more evident on the response to exercise than at rest.

Classification of β blocking drugs

1. According to pharmacokinetic properties

a. Lipid soluble: Propranolol, metoprolol, oxprenolol & labetalol

They undergo extensive first pass metabolism.

*They readily cross cell membranes, so have large apparent V_d, they readily enter CNS.

b. Water soluble atenolol, sotalol & nadolol.

They are less subjected to liver metabolism, excreted unchanged by kidney, their $t_{1/2}$ are greatly prolonged in renal failure.

They are less widely distributed & less penetration to CNS.

2. According to pharmacodynamic properties

a. With partial agonist effect (Intrinsic sympathomimetic effect, ISA)

oxprenolol, pindolol, acebutolol & esmolol.

In addition to blocking effects, they are capable of a low degree of activation i.e. they have both agonist & antagonist action (partial agonist activity).

*They cause less fall in resting heart rate than pure antagonists & are less effective in angina

*Their abrupt withdrawal may be less likely to lead to a rebound effect as there may be less up-regulation of receptors.

b. With membrane stabilizing effect (quinidine or local anesthetic like effect) oxprenolol, propranolol, acebutolol, esmolol, carvedilol

*This effect is unimportant in clinical doses, but relevant in overdose.

3. According to selectivity to receptors

a. β1-selective (cardio selective) have higher affinity to cardiac β1 receptors include: atenolol, acebutolol, metoprolol, esmolol, bisoprolol.

b. Non-selective (β1 + β2) blockade: propranolol, oxprenolol, pindolol, sotalol, timolol.

c. Non-selective β blockade + α1 blockade: labetalol, carvedilol.

Differences between selective & non-selective β blockers

1. β1 blockers are less likely to cause bronchoconstriction (theoretically), but in practice, only few available β1 blockers are sufficiently selective to be safely recommended in asthma.
2. β1 blockers can be used in diabetic patients
3. Both classes can precipitate heart failure

Clinical uses of β blockers

1. CVS- angina pectoris, hypertension, cardiac arrhythmias, myocardial infarction

2. Endocrine uses- hyperthyroidism, phaeochromocytoma

3. CNS- anxiety, migraine prophylaxis, essential tremor, alcohol & opioid acute withdrawal symptoms

4. Eye- in glaucoma- betaxolol & timolol eye drops

Adverse effects of β blockers

1. bronchoconstriction
2. cardiac failure
3. incapacity for vigorous exercise
4. hypotension when the drug is given after myocardial infarction
5. reduced peripheral blood flow especially with non-selective blockers, leading to cold extremities, intermittent claudication may be worsened
6. reduced blood flow to liver & kidneys, reducing metabolism, biliary & renal elimination of drugs, so is clinically significant when there is hepatic or renal disease
7. hypoglycemia with non-selective blockers, **they impair sympathetic homeostatic mechanism for maintaining blood glucose levels & recovery from hypoglycemia is delayed**

*This is important in diabetes & after substantial exercise

*The symptoms of hypoglycemia (anxiety & palpitation) which are mediated by sympathetic nervous system will not occur except cholinergic sweating, so the patient may miss warning symptoms of hypoglycemia & slip into coma

*β1 blockers are preferred in diabetes

8. HDL-cholesterol falls & plasma TGs are elevated during chronic treatment with non-selective β blockers. So selective blockers are preferred

Note

Abrupt withdrawal of β blockers can be dangerous in angina pectoris & after myocardial infarction, so withdrawal should be gradual. This phenomenon is least common with partial agonists.

Drug interactions

1. Enzyme inhibitors like cimetidine cause increased plasma concentration of β blockers
2. Enzyme inducers reduce plasma concentration
3. β-blockers reduce their own metabolism & of other drugs by decreasing hepatic blood flow
4. NSAIDs- attenuate antihypertensive effect of β blockers due to inhibition of formation of renal vasodilator PGs leading to sodium retention
5. β- blockers potentiate effect of other antihypertensive drugs like; Ca^{+2} channel blockers, α blockers
6. Non-selective β- blockers potentiate hypoglycemia of insulin & sulphonylureas
7. Should not be given with verapamil because both have negative inotropic & chronotropic effects

Use of β blockers in pregnancy

They are used in pregnancy related hypertension including preeclampsia.

Both lipid & water soluble drugs cross placenta, causing bradycardia & hypoglycemia of fetus

*they are not teratogenic

*some studies suggest they cause intrauterine growth retardation

Individual β blockers

A. Propranolol (Inderal)

Is the prototype of β blocking drugs, is non-selective, $t_{1/2}$=3-6h

Pharmacological effects

1. reduces heart rate, decreases force of contraction, suppresses

impulse conduction through AV node leading to reduction in CO

2. suppresses renin secretion
3. bronchoconstriction
4. VC- by blocking β2 receptors on certain BV
5. inhibition of glycogenolysis

Pharmacokinetics

Is highly lipid soluble, readily cross membranes, well absorbed following oral administration, undergoes extensive first pass metabolism, so less than 30% of each dose reaches systemic circulation. Is widely distributed to all tissues & organs including CNS. Is metabolized by liver & excreted in urine.

Therapeutic uses

1. hypertension
2. angina pectoris
3. cardiac arrhythmia
4. myocardial infarction
5. migraine
6. stage fright

Adverse effects bradycardia, AV block, heart failure, rebound cardiac excitation (abrupt withdrawal), bronchoconstriction, inhibition of glycogenolysis, depression, insomnia, nightmares & hallucinations.

Precautions & contraindications

1. severe allergy- in anaphylaxis
2. diabetes mellitus
3. heart failure, AV block, sinus bradycardia
4. bronchial asthma

5. patient with history of depression

B. Atenolol (Tenormin)

Is cardio-selective, $t_{1/2}$=6-9h, is water soluble, 90% of absorbed drug is excreted by kidney, so dose adjustment is required in renal impairment. Has less CNS side effects, less bronchoconstriction & does not interfere with glycogenolysis.

C. Metoprolol: is cardio-selective, $t_{1/2}$=3-4h, is moderately lipid soluble, causes minimal bronchoconstriction & does not interfere with glycogenolysis.

D. Bisoprolol: is cardio-selective more than atenolol, is relatively lipid soluble, $t_{1/2}$=11h.

E. Timolol: is non-selective, administered topically to decrease IOP.

F. Esmolol: is used for emergency i.v. therapy of SVT (because of short $t_{1/2}$=10-15min), in arrhythmia associated with thyrotoxicosis, peri-operative hypertension, MI.

G. Sotalol: for ventricular arrhythmias

H. Butoxamine: is a selective β2 blocker with no obvious clinical application.

Combined β1 &α- adrenoceptor blocking drugs

1. Labetalol: is used parenterally in emergency reduction of BP.

2. Carvedilol: antagonizes catecholamine action on β receptors more potently than on α receptors.

Indirect acting anti-adrenergic agents

1. Adrenergic neuron blocking agents- decrease NA release

2. Centrally acting α2 agonists- act centrally in CNS to reduce outflow of impulse along sympathetic nerves

I. Adrenergic neuron blocking drugs

Are taken up into adrenergic nerve endings by active NA reuptake mechanism. They act pre-synaptically to reduce release of NA from

sympathetic neurons, e.g.: **Reserpine, Guanethidine**, which are rarely used nowadays in hypertension.

II. Centrally acting α2 agonists

A. Clonidine (Catapress)

Is an agonist to α2 receptors (postsynaptic) in brain, stimulation of which suppresses sympathetic outflow & decreases BP.

*At high doses, it activates peripheral α2 adrenoceptors (presynapyic auto receptors) on adrenergic nerve endings, these mediate negative feedback suppression of NA release.

Uses

1. hypertension (decreases CO & VD)
2. low doses for prophylaxis of migraine
3. low doses for menopausal flushing
4. withdrawal from opioid, alcohol & tobacco

Side effects: drowsiness, sedation, dry mouth, rebound hypertension on abrupt or even gradual withdrawal, so the drug should be withdrawn slowly over 2-4 days.

*This condition subsides within 2-3 days

B. Methyldopa (Aldomet)

Acts primarily in brain stem vasomotor centers. It is converted to α methyl NA (an α2 agonist).

***It is only indicated in hypertension**

Side effects

1. CNS sedation, nightmares, depression, involuntary movements

2. GIT: nausea, flatulence, constipation, sore or black tongue

3. Positive coomb's test in 10-20% of patients taking methyldopa chronically, the test turns positive between 6^{th}-12^{th} month of treatment.

*Only 5% of positive coomb's test develops hemolytic anemia

4. leucopenia, thrombocytopenia, hepatitis

5. Gynaecomastia & lactation due to interference with dopaminergic suppression of prolactin secretion

6. Failure of male sexual function secondary to sedation

***Methyldopa is no longer a drug of first choice in treatment of hypertension, but it is still used in obstetrics for hypertension of pregnancy because of its safety profile.**

8. Drugs in Angina Pectoris

Angina: is a syndrome characterized by squeezing chest pain, due to myocardial ischaemia that results from imbalance between myocardial oxygen demand (consumption) and oxygen supply. The cause is narrowing of coronary arteries due to spontaneous spasm or atheromatous plaque that impairs endothelial function and reduced release of nitric oxide (NO) which is the main physiological vasodilator normally produced by endothelial cells.

Drugs aim to: decrease the myocardial O_2 consumption (demand) and / or improve the myocardial O_2 supply.

I. Organic Nitrates

Examples: glyceryl trinitrate (nitroglycerin), Isosorbide dinitrate, isosorbide mononitrate.

A. Mechanism of action and effects:

They relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide (NO). This process requires a presence of free SH groups. Nitric oxide activates the soluble guanylate cyclase and increases the cells' cyclic guanosine monophosphate (cGMP) .This is the second messenger which alters Ca^{+2} fluxes in the cells and decreases intracellular Ca^{+2} levels resulting in vascular smooth muscle relaxation and vasodilatation.

They mainly **dilate large veins**, which results in pooling of blood in the veins. This reduces venous return and left ventricular filling pressure. The resultant decrease in the ventricular wall tension (preload), reduces cardiac work and decreases myocardial oxygen consumption.

They dilate coronary arteries and relax coronary spasm or vasoconstriction and improve myocardial perfusion.

- Relief of chest pain by nitrates does not prove the diagnosis of angina pectoris because they can relax smooth muscle in the bronchi, oesophagus, gall bladder and biliary tract and can relieve chest pain due to spasm of smooth muscle of these organs.

B. Side Effects: are direct results of their vasodilating actions.

1. Postural hypotension, dizziness, fainting and syncope. The patient should remain supine and if symptoms are severe he should also spit out or swallow the remainder of the tablet.
2. Reflex tachycardia 3. facial flushing 4. Throbbing headache: Tolerance to headache develops quickly but re-occurs after a brief nitrate- free period. 5. Over doses can cause methaemoglobinaemia, due to oxidation of iron in haemoglobin to ferric ions.

C. Tolerance (tachyphylaxis):

Continuous administration of nitrates, results in **diminished vasodilatation and antianginal effect** , Possibly **because of depletion of free SH groups** in vascular smooth muscle cell.

It **does not occur with short-acting** preparations as sublingual glyceryl trinitrate, but mostly **occurs with long- acting** preparations as isosorbide mononitrate, or when glyceryl trinitrate is administered by prolonged I.V infusion.

Tolerance **develops very quickly** (within 24 hours), and **wears off quickly** after a brief nitrate-free period and can be prevented by providing a daily nitrate- free interval to restore sensitivity to the drug. This interval is typically **8-10- hours** at night. I.e. skin patches are removed at night and worn at morning or isosorbide mononitrate is administered at lunch and in the morning, to allow nitrate-free period during the night.

1. **Glyceryl trinitrate :**

- is the prototype of the group
- is well absorbed from the mucosal surface of the mouth and when administered sublingually, produce its effect within few minutes, so the sublingual route is preferred to terminate acute angina attack .By this route the effective duration of action is short (about 30 minutes).
- is well absorbed through the skin, and a more sustained (prolonged) effect can be achieved by applying it as a transdermal patch.
- If the tablet (formulated for sublingual route) or saliva that contains the dissolved tablet, is swallowed, the drug will be ineffective (systemic bioavailability is very low) because of extensive ^{1st} pass metabolism in the liver. Because of FPM, the oral dose is much higher than this required by sublingual route.
- The active substance in the tablet is volatile, and once a bottle of the tablets has been opened its shelf life (effectiveness) is quite short, because of evaporation. The patient must be aware of this if their tablet is no longer gives them the usual headache.

Uses:

a. acute attack of angina pectoris
b. rapid prophylaxis before exertion
c. Long term prophylaxis in chronic angina as skin patches or sustained-release oral tablets
d. congestive heart failure

2. **Isosorbide dinitrate** : Uses 1- treatment of angina 2- prophylaxis of chronic angina 3-congestive heart failure and left ventricular failure.
3. **Isosorbide mononitrate :** has similar pharmacological actions but longer-duration, slower onset , much less hepatic 1stpass metabolism and more

reliable systemic bioavailability, than glyceryl- trinitrate .It is taken orally for prophylaxis in chronic angina

II. Nicorandil

is an arterial and venodilator, reduces preload and after load so reduce cardiac work and O2 consumption. It liberates NO and increases the level of cGMP which causes vasodilatation. It also activates and opens K^+ channels in vascular smooth muscle cell's membrane to allow K^+ efflux (exit) which leads to hyperpolarization that reduces Ca^{+2} entry and induces vasodilatation

It is administered orally and it is an alternative to nitrates in patients who develop tolerance, or to other classes when these are contraindicated.

III. Calcium Channel Blockers

1. Dihydropyridines: ex: Nifedipine, Amlodipine, Felodipine
2. Non-dihydropyridines ex: Diltiazem, Verapamil

Mechanism of Action: They Block Ca^{+2} channels and inhibit calcium entrance into cardiac and smooth muscle cells of coronary and systemic blood vessels. They decrease coronary vasoconstriction or spasm and improve myocardial perfusion; particularly useful in angina due to coronary artery spasm.

They dilate arterioles, decrease the blood pressure, peripheral resistance (after- load) so, and reduce the myocardial O_2 demand.

Selectivity between heart and vascular smooth muscle varies.

Nifedipine is relatively selective to calcium channels in vascular smooth muscle and it is mainly an arteriolar vasodilator.

Verapamil and Diltiazem:

Show greater effect on the calcium channels in the heart and a weaker effect as an arteriolar vasodilator, than nifedipine. They decrease heart rate and myocardial contractility (negative inotropic effect) which reduces myocardial O_2 requirement.

They have anti-arrhythmic effect because they decrease the rate of firing of SA node and slow cardiac AV conduction, so useful in treatment of supraventricular tachycardia (SVT) and in decreasing ventricular rate in case of atrial fibrillation and flutter.

They are contraindicated in patients with bradycardia and second or third – degree heart block, because of their negative effect on myocardial conducting and contracting system.

Their co-administration with β blockers potentiates the AV block and can lead to heart failure.

Uses:

1. Prophylaxis in chronic angina 2. Hypertension 3. Raynaud's disease 4. migraine prophylaxis 5. Verapamil and diltiazem also used in atrial fibrillation **,** flutter and SVT

Side Effects: (are extensions of their pharmacological actions)

- headache, flushing ,dizziness ,peripheral (ankle) oedema, Constipation
- nifedipine can cause hypotension with reflex tachycardia and palpitation, diltiazem and verapamil can cause bradycardia .

IV. Beta Blockers

decrease myocardial O_2 requirement at rest and during exercise, because they decrease the heart rate, blood pressure and myocardial contractility.

are useful in chronic prophylaxis for exercise- induced angina .

Members that possess intrinsic sympathomimetic activity are less effective in angina.

They should not be withdrawn abruptly, but the dose should be gradually tapered over 5-10 days to avoid risk of rebound angina.

They are contraindicated in angina due to coronary artery spasm.

V. **Antiplatelet:** drugs that inhibit platelet aggregation are *given* incombination with antianginal drugs to Prevent progression to myocardial infarction (MI) and to patients who survive after MI to prevent recurrence.

Low dose (75 – 325 mg daily orally) inhibits platelets thromboxane A2.

Clopidogrel: inhibits ADP- dependent platelets aggregation.

Abciximab: monoclonal antibodies bind to the glycoprotein lla/lllb receptors and prevent binding of fibrinogen to these receptors which are the final pathway of platelets aggregation.

9. Histamine and antihistamines

Introduction Histamine is an endogenous substance, widely distributed in the body, also called “Autacoid” or local hormone, because it acts locally at the site of release.

1. Synthesis: is synthesized in the tissue from L-histidine by decarboxylation
2. Distribution: presents mainly in the skin, lung and gastrointestinal tissues, as these tissues are in direct contact to the outside of the body. It’s also stored near blood vessels and in the CNS.
3. Release: histamine is usually released with other substances as serotonin, cytokines, leukotriens, prostaglandins and Platelets activating factors.

Factors stimulating histamine release:

1. Antigen-antibody (IgE) reaction on the surface of the mast cells and blood basophils (immediate hypersensitivity reaction), this will lead to activation of proteolytic enzymes and increase the influx of calcium to the inside of the cell causing cell degranulation and histamine release
2. Drugs induce release: drugs as morphine, codeine, d-tubocurarine and guanethidine can release histamine probably by displacement from its cellular binding sites.
3. Other substances as snakes and insects venom and radiation can release histamine

4. Metabolism: the released histamine is inactivated by histaminase (diamine oxidase) and by histamine methyltransferase enzyme present in various tissues.
5. Histamine receptors: three types of receptors include H1, H2, and H3

   H1- receptors: mainly present in intestinal and bronchial smooth muscles (stimulation increases intracellular calcium).

H2-receptors: Gastric mucosa (stimulation increases cAMP)

H1+H2: the combination is mainly present in the blood vessels and

H3 : mainly in the CNS, it probably regulates histamine release

Physiological role:

1. Regulation of microcirculation in arterioles and capillaries
2. Control of gastric acid secretion
3. Neurotransmission
4. Mediation of pain and itching by affecting sensory nerve endings
5. Endocrine regulation and control of hormone release

Role in disease state:

- Allergic rhinitis (hay fever)
- Bronchial asthma
- Urticaria and eczema
- Contact dermatitis
- Food allergies

In all these diseases condition histamine is usually released in combination with other mediators

I. Pharmacological effects of histamine:

1. Cardiovascular system: histamine causes fall of blood pressure, has positive inotropic and chronotropic effects, causes flushing of the face (cutaneous vasodilatation). It also causes throbbing headache due to cerebral vasodilatation. The vasodilator effect of histamine is probably mediated by the release of nitric oxide (NO) from the endothelium of the blood vessels. The dilation of capillaries by histamine lead to increase vascular permeability and tissue swelling

2. Respiratory System: Bronchial smooth muscle contraction mediated by H1 receptors stimulation, it also increases secretory activity and prostaglandins release.
3. Histamine causes increase in catecholamine release from the adrenal gland
4. Intradermal injection of histamine leads to red line due to vasodilatation, flare due to axonal reflex and wheal due to edema formation (triple response). Histamine injected locally also causes pain and itching due to irritation of sensory nerve ending
5. Anaphylactic reaction: Rapid and extensive release of mediators which may be fatal. Introduction of specific antigen usually in food or injected materials into sensitized individuals causes rapid release of mast cell contents. This leads to intense bronchospasm and severe hypotension which might cause death. All mediators involved in this reaction.

Sodium cromoglycate (cromoglicate):

Inhibits histamine release from mast cells, also reduce allergic reactions and bronchial hyper-reactivity. Useful in the prophylaxis of bronchial asthma. It is not absorbed when given orally, so it is given by inhalation. Also useful in allergic rhinitis by nasal drops.

II. **Antihistamines**

A. Classification:

1. H1- antagonists (blockers), also called conventional antihistamines, examples; chlorpheniramine, diphenhydramine, promethazine and cyproheptadine.
2. Non-sedating H1-antihistamines such as terfenadine, astemizole and loratadine
3. H2-antagonists: as cimetidine, ranitidine and famotidine

I. H1-antanonists:

Examples; diphenhydramine, chlorpheniramine, cyclizine and promethazine are receptors blocking agents compete with histamine at H1 receptors, they have no effect on histamine release

A. Pharmacokinetics:

Are well absorbed when given orally with a peak plasma level at about 1 hour following ingestion.They are metabolized by the liver with a half-life of 3-4 hours

B. Clinical uses:

1. Allergic conditions; as allergic rhinitis and urticaria,
2. Motion sickness; antihistamines as diphenhydramine and cyclizine are effective in the treatment of motion sickness probably due to their anticholinergic effect, which cause reduction of fluid in the inner ear
3. Diphenhydramine is useful in the treatment of Parkinson's disease again due to its anticholinergic effect
4. Sedation, most of these drugs have a potent sedative action, this can be useful in the treatment of anxiety associated with allergic diseases, and on the other hand excessive sedation can be considered as an adverse effect.
5. Anaphylactic shock :usually antihistamines are given in combination with other drugs such as adrenaline and corticosteroids
6. Antihistamines are not useful in bronchial asthma due to the anticholinergic effects

C. Adverse effects

1. sedation, drowsiness, dizziness fatigue, tremor and nervousness
2. Antimuscarinic effect; which lead to dryness of mouth, blurring of vision , retention of urine
3. others as agranulocytosis

II. Non-sedating antihistamines:

Examples: terfenadine, fexophenadine, astemizole, cetrizine and loratadine

These are characterized by:

1. Non-sedating as they do not pass the blood brain barriers
2. lacking anti-musacrinic adverse effects:

Terfenadine has cardiac toxicity characterized by ECG changes as prolongation of QT interval, this toxicity is potentiated when given with enzyme inhibitor drug as erythromycin and ketoconazole

III. H2- receptor antagonists:

Examples: cimetidine, ranitidine, famotidine and nizatidine

They act by selectively binding to H2 –receptors in the stomach. They reduce hydrochloric acid secretion by gastric mucosa, they can reduce the volume of acid secretion and also modify its PH (causes increase in PH).

Both effects promote the healing of peptic ulcer.

1. Cimetidine:

Is the prototype of the group, it is useful in the treatment of peptic ulcer (both duodenal and gastric ulcers).

Cimetidine is well absorbed when given orally, with peak blood concentration reaches in 1 hour.

Adverse effects:

1. Headache, dizziness, drowsiness and tremor
2. lethargy, fatigue , confusion and hallucinations specially in the elderly
3. Gynaecomastia also occurs due to the anti-androgenic effect of cimetidine
4. Cimetidine is an enzyme inhibitor, it inhibits CYP450 types(CYP 1 A2 and CYP 3A4), therefore it may increase the serum levels of some drugs such as phenytoin, warfarin and theophylline.

10. Prostaglandins and serotonin

Objectives:

The student should be able to define the following:

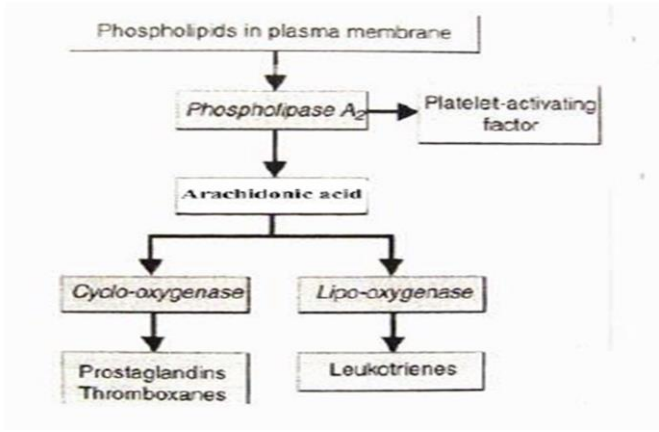
1. Arachidonic acid, Prostaglandins, Thromboxane, Leukotriens
2. Cyclooxygenase (COX1), (COX2)
3. Prostaglandin analogues

The student should be able to describe:

1. In schematic way the pathways of prostaglandins and leukotriens' synthesis.
2. The Pharmacological effects and clinical usefulness of prostaglandins on various body organs and tissues.
3. Effect of prostaglandins on platelets function.
4. Drugs, which act as prostaglandins (analogues), their clinical indications and side effects.

A. **Definition**: Eicosanoids: Prostaglandins, Thromboxane, and Leukotriens

Eicosanoids are a group of fatty acids derived basically from arachidonic acids in the cell walls. Arachidonic acid is stored in the phospholipids of the cell wall and released from the cell membrane lipids by Phospholipase A_2. The biosynthesis paths of eicosanoid are shown in Figure 1. Prostaglandins are synthesized in all tissues of the body, where they act as local hormones. Unlike true hormones which migrate in the blood to produce effect in remote places, prostaglandins act in the tissues in which they are synthesized.



Glucocorticoids act by inhibiting phospholipase A_2 through production of lipocortin-1 which leads to inhibition of Arachidonic acid formation and subsequently inhibit prostaglandins synthesis and also leukotriens. This explains the anti-inflammatory effect of glucocorticoids.

B. Metabolism of Arachidonic acid:

It is metabolized by two pathways:

1. Cyclooxygenase pathway (it can now be called prostaglandin G/H synthase). This enzyme changes the linear fatty acid into the cyclical structures of the prostaglandins, the final result of metabolism of this pathway is: 1. prostaglandins (PG) and 2. thromboxane (TXA_2). Non-steroidal anti-inflammatory drugs (NSAIDs) exert their anti-inflammatory effects by inhibiting this pathway. Cyclooxygenase is present in two forms: cyclooxygenase (COX-1) and (COX-2). The differences between these two; COX-1 is non-inducible and produced at a contant rate irrespective to physiological demand. It is present in many tissues including platelets, stomach and kidneys; COX-2 is present in macrophages, leukocytes and fibrocytes. COX-2 is induced by cytokines and endotoxins at site of inflammation (e.g. in the joints). Non-selective NSAIDs such as aspirin, diclofenac (voltaren),

indomethacin and others inhibit COX-1, while celecoxib selectively inhibits COX-2.

2. Lipo-oxygenase pathway: this results in the synthesis of leukotriens that cause increased vascular permeability, vasoconstriction and broncho-constriction and also involved in chemotactic, inflammatory and allergic conditions.

C. Types and names of Prostaglandins (PG)

1. PGH_2 2. PGD_2 3.PGE_2

4. $PGF_{2\alpha}$ 5. PGI_2 (Prostacyclin)

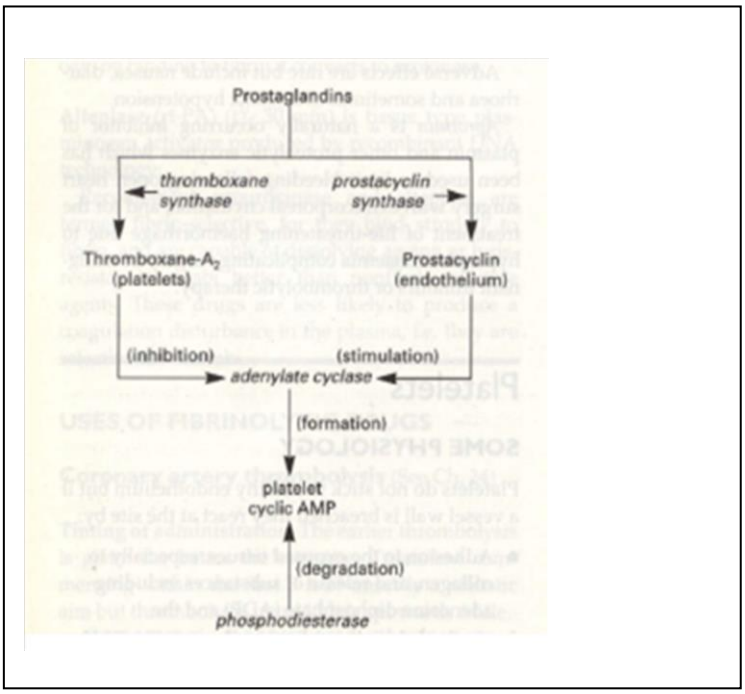
I. Basic Pharmacology of Prostaglandins:

It seems that there are specific receptors through which PGs produce their effects, for example, PGI_2 (prostacyclin) inhibits platelets aggregation through binding to receptors that specially activate adenylate cyclase. This leads to increase cAMP which in turn activates specific protein kinases. Calcium ion is involved in this process.

A. Effect of Prostaglandins on smooth muscles:

1. Vascular smooth muscle: human arteriolar vascular smooth muscle is relaxed by PGE_2 and PGI_2. Thromboxane (TXA_2) and $PGF_{2\alpha}$ act as a vasoconstrictor.
2. Gastro-intestinal tract: PGH_2 and $PGF_{2\alpha}$ cause contraction of longitudinal muscle of the intestine. PGE_2 relaxes the circular muscle. Prostaglandins in general cause colicky cramps in the abdomen.
3. Respiratory airways: PGE_2 and PGI_2 relax smooth muscle. TXA_2 and $PGF_{2\alpha}$contract it.
4. Genito-urinary tract: PGE_2 and $PGF_{2\alpha}$ cause contraction of the smooth muscle of genito-urinary tract.

B. Effect on platelets: PGI_2 (prostacyclin) inhibits platelets aggregation. TXA2 strongly facilitates platelets aggregation. Cyclic AMP plays a key role in platelets activity. High concentrations of intra-platelets cyclic AMP inhibit platelets adhesion, aggregation and low concentrations of cyclic AMP have the opposite effect. The effect of prostaglandins on platelets activity is summarized in Figure-2.



C. Effect on central and peripheral nervous system:

1. Fever: PGE_1 and PGE_2 increase body temperature. Recently, pyrogens have been shown to promote the synthesis and release of PGE_2. This is blocked by aspirin and other NSAIDs.
2. Sleep: PGD_2 is involved in sleep
3. Neurotransmission: PGE inhibits release of noradrenaline from the nerve ending. Thus the vasoconstriction observed after treatment with NSAIDs may be due to increased released noradrenaline as well as inhibition of endothelial synthesis of vasodilator prostaglandins (PGE_2 and PGI_2).

II. Clinical Pharmacology of Prostaglandins:

1. Female reproductive system:

a. Abortion: PGE_2 and $PGF_{2\alpha}$ are well known for their oxytocic action. They can terminate pregnancy at any stage in about 80% of cases by promoting uterine contraction. Intra-amniotic administration of $PGF_{2\alpha}$ has about 100% success rate with fewer and less severe adverse effects than I.V. administration.

b. Facilitation of labour: PGE_2 and $PGF_{2\alpha}$, are theoretically superior to oxytocin in patients with preeclampsia, cardiac and renal disease because they have no anti-diuretic effect.

c. Dysmenorrhea: This is due to increased endometrial synthesis of PGE_2 and PGF_{α} during menstruation with contraction of the uterus that leads to ischemic pain. NSAIDs relieve this pain through inhibition of prostaglandins release.

2. Cardiovascular system: PGI_2 lowers peripheral and coronary resistance. It has been used to treat pulmonary hypertension and also useful in the treatment of Raynaud's phenomena.

a. Thrombosis: TXA2 promotes platelets aggregation, PGI_2 inhibits it. (see figure 2.)

b. Patent Ductus Arteriosus: Patency of fetal ductus arteriosus is dependent on PGE_2 and PGI_2 synthesis. In certain types of congenital heart disease, pulmonary atresia, it is important to maintain the patency of the ductus arteriosus before surgery. This can be achieved by the administration of prostaglandins. In delayed closure of the ductus arteriosus cyclooxygenase inhibitors (e.g. indomethacin) can be used.

3. Respiratory system: PGE_2 is a powerful bronchodilator. PGD_2 and TXA_2 are strong bronchoconstrictors. Corticosteroids which inhibit prostaglandins synthesis play a role in treatment of bronchial asthma.
4. GIT: PG has a cytoprotective effect and used in NSAIDs- induced gastric ulceration.
5. Immune system: PGE_2 has been proposed as an inflammatory mediator in arthritis. Therefore, aspirin through inhibition of cyclooxygenase pathway of prostaglandins synthesis has a role in the treatment of arthritis.

Synthetic Analogues of Prostaglandins:

1. PGI_2: epoprostenol (inhibits platelets aggregation)
2. PGE_1: alprostadil used to maintain the patency of the ductus arteriosus in neonate.
   misoprostol used for prophylaxis of peptic ulcer associated with NSAIDs
3. PGE_2 : dinoprostone: to induce labour.
4. $PGF_{2\alpha}$: carboprost: termination of pregnancy.
   bimatoprost : ophthalmic drops for glaucoma.
   latanoprost : ophthalmic drops for glaucoma

Serotonin

Objectives:

The student should be able to describe:

1. What is serotonin?
2. Basic Pharmacology of serotonin

   Chemistry and Pharmacokinetic

   Mechanism of action

   Effect on organs and tissues (CNS, CVS, airways, and GIT.)
3. Clinical Pharmacology of Serotonin

a. Serotonin Agonists: Dexfenfluramine, Sumatriptan, fluoxetine (serotonin reuptake inhibitor)

b: Serotonin Antagonists:

- *P*-chlorophenylalanine
- *P*-chloroamphetamine (these drugs are too toxic for general use)

Cyproheptadine

Ketanserine

Ondansetron

A. Definition

It was noticed when a blood is allowed to clot, a substance is released which causes vasoconstriction. This substance is called serotonin. Serotonin is also identified in carcinoid tumours of the enterochromaffin cells in the GIT. In this condition signs of high level of serotonin are noticed.

B. Chemistry and Pharmacokinetic:

Serotonin is available in plants like (bananas), animal tissues, venoms and stings. The precursor of serotonin is the amino acid (L-tryptophan). After synthesis it is either stored or rapidly inactivated by monoamine oxidase. In human, over 90% of serotonin in the body is found in enterochromaffin cells

in the GIT. Serotonin is also found in platelets, brain stem (it is involved in mood, sleep, appetite, and temperature regulation, perception of pain, blood pressure regulation and in vomiting reflexes). It is also involved in depression, anxiety and migraine. Serotonin is metabolized by monoamine oxidase and the stored serotonin is depleted by reserpine (as the case with catecholamine)

C. Pharmacodynamics of serotonin:

Serotonin exerts its effect through various receptors. There are 7 subtypes of these receptors (5HT receptors) numbered from $5HT_1$ to $5HT_7$.

Effect on organs and tissues:

1. Nervous system:

Serotonin acts as a neurotransmitter; $5HT_3$ receptors available in the medullary vomiting center as well as in the GIT participate in the vomiting reflex. Serotonin is a potent stimulant of pain and itching and is involved in some of pain-associated insect or plant stings.

2. Airways:

Serotonin has a small direct stimulant effect on smooth muscle of bronchi, however, high levels of serotonin found in carcinoid tumour result in episodes of bronchoconstriction.

3. Cardiovascular system:

Serotonin has a direct vasoconstriction effect on vascular smooth muscle (mediated through $5HT_2$), however, it causes vasodilatation of blood vessels of skeletal muscle and the heart. Serotonin has also a positive chronotropic and ionotropic effect which has no clinical significance. Serotonin causes platelets aggregation.

4. Gastrointestinal tract:

Serotonin causes contraction of the smooth muscle of the GIT, facilitating peristalsis (this effect is mediated through $5HT_2$ receptors). Activation of $5HT_4$ receptors causes increased acetylcholine release and thereby mediates a motility-enhancing or "prokinetic" effect.

Clinical Pharmacology of Serotonin:

Serotonin has no clinical application as a drug

a. Drugs with agonist activity on serotonin receptors:

1. Lorcaserin is a selective 5-HT_{2C} receptor agonist, and it is licensed by the American Food and Drug Administration (FDA) in 2012 for the use as appetite suppressant in obesity. It is found safe apart from headache and dizziness.
2. Dexfenfluramine: This is a selective 5HT agonist which was widely used as appetite suppressant (**this drug is relatively toxic and was withdrawn from the market**).
3. Sumatriptan: is a selective agonist acting on $5HT_{1D}$ and $5HT_{1B}$ receptors in the brain. It is very effective in the treatment of migraine headache. As a result of its effect on blood vessels, sumatriptan administration is associated with chest discomfort which occurs in 1–5% of patients, and chest pain has been reported, probably because of the ability of these drugs to cause coronary vasospasm. It is therefore contraindicated in patients with coronary artery disease and in patients with angina.
4. Tegaserod, a newer 5-HT_4 partial agonist, is used for irritable bowel syndrome with constipation. (Withdrawn from the market 2007 for safety issues; cardiac)
5. Fluoxetine (a selective serotonin-reuptake inhibitor). This drug is useful in treatment of depression and other behavioral disorders.

b. Drugs with antagonist activity on serotonin receptors:

1. Cyproheptadine: resembles the phenothiazine antihistaminic agents in chemical structure and has a potent H_1-receptor blocking as well as 5-HT_2 blocking actions. It has also significant antimuscarinic effects and causes sedation.

The major clinical applications of cyproheptadine are in the treatment of the smooth muscle manifestations of carcinoid tumor and in cold-induced urticaria. It is also useful as appetite stimulant.

2. Ketanserine : This drug has both alpha blocking and $5HT_2$-receptor blocking activity. It has, in addition, anti-platelets aggregation effect and antihypertensive effect.
3. Ondansetron: This drug has 5HT3 antagonist effect, and proved to be useful in the treatment of vomiting associated with chemotherapy administration.
4. Ergot alkaloids: The mechanism of action of these alkaloids Is due to their action on several types of receptors. Their effects include agonist, partial agonist, and antagonist actions at alpha adrenoceptors and serotonin receptors (especially 5-HT_{1A} and 5-HT_{1D}; less for 5-HT_{1C}, 5-HT_2 and 5-HT_3).

11. Sedatives, Hypnotics and Anxiolytics

Anxiolytics: the drugs that relieve anxiety with little CNS depression

Sedatives: the drugs that quiet the excited or agitated patient

Hypnotics: the drugs that induce sleep and useful in the treatment of insomnia.

Drugs in this group include benzodiazepines, barbiturates, buspirone, chloralhydrate, and meprobamate

Other drugs include beta-blockers and H1-antihiatamines

I. Benzodiazepines:

Examples: diazepam, lorazepam, temazepam and nitrazepam , chlordiazepoxide, oxazepam. All these drugs act by the same mechanism and only differ in pharmacokinetic parameters as the half-life and route of metabolism

A. Mechanism of action of benzodiazepines:

The benzodiazepines are similar in chemical structure to the inhibitory neurotransmitter gamma amino butyric acid (GABA), an inhibitory neurotransmitter. They act by binding to the benzodiazepine site at the GABA receptors, which leads to the opening of chloride ion channels and the potentiation of the action of GABA. So benzodiazepines potentiate the actions of GABA. There are different sub-types of benzodiazepine receptors which mediate different actions. Benzodiazepines act on the brain reticular system and the limbic system. There are endogenous substances that can bind to benzodiazepine receptors and probably relieve anxiety. In addition there are endogenous substances called inverse agonists that can combine to the benzodiazepine receptors but produce anxiety as carbolines.

Benzodiazepine antagonist as flumazenil can also combine with benzodiazepine receptors and antagonize all the actions of benzodiazepines.

B. Pharmacokinetics of benzodiazepines:

Well absorbed when given orally. The absorption of intramuscular injection is less rapid and irregular, so it is not preferred to be given by this route while the intravenous injection produces rapid effect and useful in emergency. The benzodiazepines are highly protein bound (85%). The major site of metabolism is the liver, the metabolism include chemical biotransformation followed by conjugation with glucuronide to be excreted in the urine. Liver disease leads to reduced rate of metabolism and increased toxicity, in this case lorazepam and oxazepam are preferred as they are metabolised by conjugation only. Most of the metabolites of benzodiazepines are pharmacologically active and this leads to prolongation of their pharmacological action. The metabolism of benzodiazepines decreases with age, so the dose should be reduced in the elderly patients. Also the dose should be reduced in patients with liver disease.

C. Clinical uses of benzodiazepines:

1. Anxiety and panic state: both acute and chronic anxiety can be treated with benzodiazepines , the lowest effective dose should be used for the shortest possible time to avoid tolerance and dependence, drugs used include diazepam, chlordiazepoxide and lorazepam
2. Insomnia (difficulty to go to sleep), benzodiazepines reduce the latency to sleep and prolonged the sleeping time. They reduce rapid eye movement (REM) sleep but to a lesser extent than other hypnotics. Drugs with shorter half-life as nitrazepam are preferred to avoid prolonged sedation

3. Muscle relaxation, due to inhibition of polysynaptic reflexes in the spinal cord, they are especially useful in pain and muscle spasm associated with injuries and inflammatory condition, diazepam is usually used. Benzodiazepines are also useful in tetanus to relieve muscle spasm
4. Anticonvulsants in status epileptics and in febrile convulsions in children, usually given intravenously or rectally as diazepam or lorazepam
5. In epilepsy as antiepileptic, like clonazepam which is useful in some form of epilepsy specially in children
6. Pre-an aesthetic medications to reduce anxiety before surgical operations and to produce anterograde amnesia (loss of memory after drug administration) for the procedure
7. Alcohol and hypnotics drug withdrawal state, to relieve the symptoms of withdrawal as chlordiazepoxide and diazepam

D. Adverse effects of benzodiazepines:

1. On the central nervous system, cause sedation, drowsiness, ataxia and amnesia, slowing of reaction time impair driving skill and predispose for accidents
2. Rapid intravenous injection may lead to respiratory and cardiovascular depression which may be fatal in patients with cardiac or respiratory diseases
3. Dependence and tolerance: prolonged use of benzodiazepines can lead to both physical and psychological dependence and withdrawal symptoms (occur when the patient suddenly stops taking the drug) characterized by severe anxiety, insomnia, tremor and convulsions associated with nausea, vomiting and loss of appetite. It is therefore

recommended that these drugs stopped gradually by dose reduction with time specially after prolonged use

4. Overdose lead to CNS and respiratory depression followed by coma, which is much less severe than barbiturate. Benzodiazepines rarely cause death in overdose when ingested alone, but death might occur when taken with other CNS depressant drugs
5. Drugs interaction, benzodiazepines potentiate the effect of other CNS depressants as alcohol, antihistamines and barbiturates.

E. Benzodiazepine antagonist

Flumazenil

acts by binding to benzodiazepine receptors it can reverse the effects of benzodiazepine overdose and toxicity. It should be given by intravenous injection. Usually repeated doses are needed because it has a short half-life. Can also be used to terminate the benzodiazepines action when used in endoscopy and intensive care.

Flumazenil can precipitate withdrawal symptoms in benzodiazepines dependent patients and it may cause convulsion, so should be given with caution in these patients. It may cause brief anxiety

F. Drugs with anxiolytic effects

1. Barbiturates

Example; phenobarbitone, primidone, pentobarbitone and thiopentone

Mechanism of action: Like benzodiazepines enhance the action of GABA, but they bind to different sites on the GABA-receptors/chloride channels, and their action on the CNS is less specific leading to more CNS depression

Barbiturates are less commonly used as hypnotics, sedatives or anxiolytics

Because:

a. Barbiturates have low therapeutic index (can cause respiratory and cardiovascular depression even when given in therapeutic doses)
b. Can rapidly cause strong physical dependence with withdrawal symptoms
c. They are potent enzyme inducers which may lead to wide interaction with other drugs
d. Highly toxic in overdose and frequently lead to death due to respiratory and CNS depression.

But still barbiturates have other clinical uses

A. Pharmacokinetics:

Rapidly absorbed after oral administration with variable plasma protein binding, are metabolized by the liver and can induce hepatic drug metabolizing enzymes

B. Clinical uses:

1. epilepsy as antiepileptic in tonic-clonic epilepsy (oral phenobarbitone and primidone)
2. induction of anesthesia (I.V thiopentone), to make the patient unconscious quickly. Thiopentone is highly lipid soluble and acts within seconds when given intravenously
3. neonatal jaundice, as enzyme inducer (oral phenobarbitone), which induces the liver enzymes, so increases bilirubin conjugation to water soluble compound and enhances it renal excretion

C. Adverse effects:

1. hypotension and reduction of cardiac output and myocardial depression
2. drowsiness, dizziness and confusion

3. respiratory depression especially in patients with asthma and bronchitis
4. physical and psychological dependence with withdrawal symptoms as tremor, weakness , dizziness, distorted vision, delirium and convulsions in severe cases
5. Allergic reaction as skin rash
6. drug interactions; potentiate the effect of other CNS depressants and also induce metabolism of other drugs and reduce their effects

2. Meprobamate

Has sedative, hypnotic and anxiolytic effects. May cause excessive sedation and dependence liability, so it is less used in anxiety.

It is well absorbed when given orally, metabolized by the liver and has a significant enzyme inducing effect. Meprobamate is used as a muscle relaxant mainly to relieve muscle spasm by inhibiting spinal reflexes, due to potentiating the effect of GABA inhibitory transmitter in the spinal cord

Adverse effects: excessive sedation, drowsiness, dependence and withdrawal symptoms lead to insomnia, anxiety and convulsions

3. Chloralhydrate:

is used mainly as a hypnotic to induce sleep, it is given orally as solution to reduce gastric irritation and improve its bad taste. It induces sleep within half hour of oral dose. It is relatively safe in therapeutic doses but in high doses causes respiratory depression. Chloralhydrate is well absorbed from the intestine, metabolized by the liver into trichloro-ethanol (the active form of the drug) by the action of the enzyme alcohol dehydrogenase.

Used mainly as hypnotic especially in children.

It interacts with alcohol because they are metabolized by the same enzyme and this will lead to inhibition of alcohol metabolism and increase its concentration and toxicity

4. Buspirone:

   Relieves anxiety with less sedative or euphoric effect. Buspirone differs from benzodiazepines in mechanism of action. Acts as a partial agonist at serotonin 5HT1A and dopamine D2 receptors.

   Has minimal dependence and abuse potentials

   Has less psychomotor impairment effect in comparison with diazepam

   Fewer interactions with CNS depressant drugs

   Well absorbed from the GIT and extensively metabolized by the liver and highly bound to plasma proteins (95%)

   It is effective in anxiety but has no muscle relaxant or anticonvulsant effects and does not potentiate the effect of other CNS depressant drugs

5. Zopiclone

   Acts like benzodiazepines on benzodiazepines/GABA receptors. Have similar effects to benzodiazepines, causes less dependence and fewer withdrawal symptoms

6. Chlormethiazole

   is related in structure to vitamin B1 (thiamine). It may act by altering dopamine function in the brain. It is mainly useful in the treatment of withdrawal state of alcohol. It has sedative, hypnotic and anticonvulsant effects

7. Beta-blockers in anxiety:

   Beta blockers are useful in the treatment of autonomic symptoms of anxiety as tremor, palpitation and excessive sweating. The highly lipid

soluble beta-blockers as propranolol are most useful as they can pass to the brain more easily.

8. Antihistamines:

   As diphenhydramine and chlorpheniramine

   H1 antihistamine has sedative effects probably not related to their histamine antagonist effect; this can be therapeutically useful when anxiety associated with allergic disease.

   Their potent anticholinergic effect prevents their abuse.

12. Antipsychotic drugs

Also called Neuroleptics and major tranquilizers

They are effective in the treatment of schizophrenia. They are also useful in psychosis associated with depression and mania and the treatment of acutely disturbed patient.

Schizophrenia is characterized by; delusions (paranoid), hallucinations, thought disorders and abnormal behavior, social withdrawal and flat emotions

Schizophrenia was found to be associated with increase in dopamine activity in the brain, with possible role for 5HT, so drug useful in this disease are expected to modify these neurotransmitters

A. Classification of antipsychotic drugs:

1. phenothiazines: chlorpromazine, promazine, promethazine, thioridazine, trifluperazine, prochlorperazine and fluphenazine
2. butyrophenones: haloperidol, benperidol
3. thioxanthines: flupentixol, zuclopenthioxol
4. atypical antipsychotic drugs: pimozide, loxapine

B. Mechanism of action:

- Antipsychotic drugs act by blocking dopamine D_2 receptors centrally in the brain, this blockade produces the antipsychotic and antiemetic effects.
- The antipsychotics also inhibit the function of the hypothalamus, which cause loss of temperature control, galactorrhea, amenorrhea, and weight loss
- The blockade of D_2 receptors also produces the extra-pyramidal symptoms

- The anti-psychotics can also act on other receptors which include:
  alpha adrenoceptor blockade
  anti-muscarinic
  histamine-H 1 receptor blockade
  serotonin (5HT) receptor blockade

C. Drugs

1. Phenothiazines

Chlorpromazine is the prototype of this group

Mechanism of action: They have central calming effect which inhibits hallucination (D2-blockade). They can also inhibit the chemoreceptor trigger zone and the hypothalamic function. They produce powerful extra-pyramidal effects. They have also alpha-adrenoceptor blockade, this causes postural hypotension

Pharmacokinetics:

Phenothiazines have variable absorption from the gastrointestinal tract with bioavailability of only 30%. The absorption is delayed by the presence of food. Peak plasma level is reached in 2-3 hours with half-life between 2 -24 hours. They are highly lipid soluble with a wide volume of distribution. They are mainly metabolized by the liver with large number of active metabolites. Phenothiazines are highly protein bound (90-95%).

Clinical uses of phenothiazines (chlorpromazine):

a. as anti-psychotic in schizophrenia especially useful in acute episodes
b. hypomania
c. severe anxiety not responding to benzodiazepines and panic state
d. co-analgesic in chronic pain and terminal illness

e. anti-emetic, due to inhibition of CTZ useful in vomiting due to metabolic disturbances, cytotoxic drugs and radiations
f. intractable hiccup due to phrenic nerve irritation
g. allergic conditions as promethazine has a strong antihistamine effect
h. in the treatment of non-pyrogen induced fever to lower body temperature

Adverse effects of phenothiazines:

1. Anticholinergic effects; blurred vision, dry mouth, constipation and urinary retention
2. Postural hypotension due to blockade of α_1 adrenoceptors
3. Excessive sedation, drowsiness , confusion and seizures
4. Abnormal involuntary movements including tremor, dystonia and dyskinesia, this is due to blockade of dopamine effect in the brain
5. Cholestatic jaundice occurs in 2-6% of patients as an idiosyncratic reaction
6. Allergic reactions; skin rash and bone marrow suppression
7. Cardio-toxicity; cardiac arrhythmias and conduction block
8. Interaction with other drugs:
    a. can potentiate the effect of other CNS depressant drugs
    b. anti-cholinergic effect decreases the absorption of other drugs
    c. potentiate the effect of anti-hypertensive drugs
    d. they can inhibit hepatic drug metabolizing enzymes and increase the toxicity of other drugs.

2. Butyrophenones:

Haloperidol:

It is used as alternative to phenothiazine as anti-psychotic drug . It has better bioavailability of about 60%, metabolized by the liver and has no

pharmacologically active metabolites. Haloperidol causes less severe hypotension than phenothiazines, however it can cause extra-pyramidal symptoms like phenothiazines. Haloperidol can also cause leukopenia, agranulocytosis and jaundice

3. Atypical antipsychotic drugs:

Clozapine Olanzapine Resperidone

- Have similar mechanism of action to other drugs
- Cause few extra-pyramidal symptoms
- Allergic skin reactions are less common
- Clozapine is useful in schizophrenia resistant to other drugs

4. Depot preparation of antipsychotic drugs

Haloperidol Flupentixol

- Long acting form of the drug
- Contains fatty ester of the drug, which releases the drug slowly by the action of tissue esterase enzyme
- Is given every 4 weeks. It improves the patient compliance with treatment

Neuroleptic malignant syndrome

This syndrome may develop in up to 1% of patients taking antipsychotic drugs and is more common with high doses, especially in the elderly patients. Features include:

- Fever
- Confusion
- Rigidity of muscles
- Tachycardia
- Elevation of blood pressure
- Urinary retention

13. Antidepressants

A. Definition: Depression is a psychiatric illness characterized by mental and physical symptoms, including depression mode , loss of interest in normal activities, feeling of guilt, inability to take decisions, loss of confidence, loss of appetite, difficulty in sleep and suicide ideas. Depression is of two types unipolar and bipolar (manic-depression)

B. Amine theory: Depression occurs due to disturbances in the catecholamines concentrations in the brain including the reduction in serotonin, and noradrenaline in certain sites in the brain. In support of this theory is the fact that most antidepressant drugs act mainly by increasing catecholamines centrally in the brain. Reserpine, a drug which depletes catecholamines centrally in the brain can cause depression as a side effect. However depression may be caused by more complex mechanisms including genetic factors

C. Drugs useful in the treatment of depression:

1. Tricyclic antidepressants: imipramine, amitriptyline, clomipramine.
2. Second generation: mianserine, maprotiline, amoxapen , trazodone, bupropion, nefazodone and venlafaxine
3. Monoamine-oxidase inhibitors:
    a. non-selective and irreversible: phenelzine, isocarboxazid, tranylcypromine
    b. selective and reversible (MAOI-A): meclobemide
4. Selective Serotonin reuptake inhibitors: Fluoxetine, citalopram, paroxetine, Sertraline
5. Lithium : useful in manic-depression

Tricyclic-antidepressants:

Imipramine, amitriptyline, nortriptyline and clomipramine

Called tricyclic due to their chemical structure which contain three cycles

Mechanism of action: all act by inhibiting the neuronal reuptake of catecholamine (noradrenaline and/ or serotonin) centrally in the brain and increasing the brain stores of these amines. They usually take two weeks for the full clinical benefit to occur. Amitriptyline has a sedative effect in addition to the anti-depressant action, so it is useful in agitated patients. Imipramine has less sedative effect.

Pharmacokinetics:

- Intestinal absorption is slow and incomplete specially in high doses due to anticholinergic effect
- Highly lipid soluble
- Extensive first pass metabolism
- Active metabolites
- High protein binding (85-90%)

Clinical uses:

1. Depression
2. Panic attacks and severe anxiety states
3. Nocturnal enuresis in children, due to anticholinergic effect and changing sleep pattern

4. Co-analgesics: administered with analgesic drugs especially in chronic pain as it improves pain control by inhibiting pain pathway and relieving associated depression

Adverse effects:

1. Anticholinergic: dry mouth, constipation, tachycardia, retention of urine
2. CNS: tremor, sedation, confusion, insomnia, convulsions
3. Cardiovascular : postural hypotension (alpha blockade) , tachycardia, ECG changes (flat T wave, ST depression and QT prolongation), AV block
4. Allergic reactions; skin rash, cholestatic jaundice and bone marrow depression

Drug interactions with tricyclic antidepressants

1. Potentiate other CNS depressants as benzodiazepines and barbiturates
2. Potentiate the effects of monoamine oxidase inhibitors
3. Potentiate the effect of anti-muscarinic drugs
4. Reduce the antihypertensive effect of guanithidine and clonidine by inhibiting their neuronal uptake
5. Potentiate the effects of sympathomimetic amines as noradrenaline and amphetamine

2. Second generation antidepressants:

Trazodone:

Acts by antagonism at serotonin receptors (5HT-$_{2A}$ or 5HT$_{2C}$) and blocking presynaptic (alpha2) adrenoceptors and increased catecholamine secretion. It lacks anticholinergic effects and causes less interactions with drugs and is relatively safe in overdose. But it may cause seizures especially in overdose

Maprotiline:

Is a tetracyclic compound similar in action to the tricyclic compounds, has a long half-life and can be given in a single daily dose

Amoxapen:

Causes less cardiac toxicity but may cause extra-pyramidal symptoms

Nefazodone

Also lacks anticholinergic effects, but may cause hypotension, it improves sleep.

3.Monoamine oxidase inhibitors:

Irreversible and non-selective: phenelzine, isocarboxazid, tranylcypromine

They act by irreversible inhibition of MAO enzymes and increase catecholamine centrally in the brain, some of them have prolonged action even after cessation of therapy. They are only used when there is no response to other drugs. Also they take 2 weeks for clinical response to occur.

Adverse effects:

1. Atropine like action as dry mouth, blurring of vision, retention of urine and constipation
   c. CNS : anxiety, acute confusion, tremor, hyper-reflexia
   d. Others, hepatocellular necrosis, skin rash and jaundice

Drug interactions:

1. Cause severe hypertension when given in combination with amines as Adrenaline, ephedrine and amphetamine. This may lead to sub-arachnoid hemorrhage
2. Also hypertensive reaction may occur following the ingestion of tyramine containing food as cheese and banana
3. MAOIs can also inhibit the metabolism of other drugs as barbiturates and hypoglycemic agents

Reversible selective MAOIs (MAOI-A)

Meclobemide:

Inhibits MAO-A in the brain, but has no effect on MAO-B which is widely distributed in the body including the GIT. Therefore meclobemide is less likely to cause hypertensive reactions. It has also a reversible action with loss of all the activity after 24 to 48 hours following cessation of treatment.

Adverse effects:

Nausea, vomiting, dizziness insomnia and agitation

Less interaction with food and less toxicity in overdose

3. Selective serotonin reuptake inhibitors (SSRIs):

Fluoxetine, paroxetine, sertraline

Selectively inhibit serotonin uptake, they have little effect on other catecholamine like dopamine and noradrenaline. They have no effects on muscarinic, adrenergic or histamine receptors.

They have fewer adverse effects and can be given in a single daily dose due to long half life

Adverse effects:

1. Nausea, vomiting and diarrhea
2. Headache, nervousness, agitation and insomnia
3. Fewer interactions with other drugs and free from cardiovascular side effects

Lithium

Is clinically used as lithium salts like lithium carbonate. Lithium is effective in the treatment of manic-depression. The mechanism of action includes ; as a mono-valent cation Li^{+} can replace Na^{+} ions which lead to altered neuronal function, it also interacts with second messengers (G-proteins) and causes inhibition of inositol phosphate

Pharmacokinetics:

- Lithium salts as lithium carbonate converted inside the body into lithium ions (Li^{+3})
- Not bound to plasma proteins
- Low therapeutic index so requires serum level monitoring during treatment

- Diuretics reduce renal clearance

Adverse effects:

1. CNS: drowsiness, dizziness, ataxia, tremor, dysarthria coma and convulsions
2. Cardiovascular: hypotension and cardiac dysrhythmias
3. Nephrogenic diabetes insipidus (antagonizes ADH hormone)
4. GIT: nausea, vomiting and diarrhea

14. Antiepileptic Drugs

I. Definition:

Epilepsy is a chronic neurological disorder characterized by recurrent seizures.

Seizures are transient signs and/or symptoms- due to abnormal excessive neuronal activity in: some neurons (localized seizures) or all neurons (generalized seizures) in the brain

Seizures are of two types:

Convulsive seizures

Non-convulsive seizures (e.g. some types of absence seizures - petit mal epilepsy)

II. Mode of action of antiepileptic drugs

They inhibit the neuronal discharge or its spread through one or more of the following ways:

1. Reducing cell membrane permeability to ions particularly sodium (carbamazepine, phenytoin, lamotrigine, …)
2. Enhancing the activity of gamma-amino-butyric acid (GABA): the main inhibitory transmitter of the brain (GABA potentiators) e.g.

e.g. sodium valproate, barbiturates, benzodiazepines, vigabatrin, gabapentin

3. Inhibiting excitatory neurotransmitters (such as glutamate) e.g. lamotrigine

4. Calcium channel blockers e.g. gabapentin, ethosuximide, Carbonic anhydrase inhibitors (this inhibition reduces central excitability) e.g. topiramate, levetiracetam

Pharmacology of individual drugs

1. Carbamazepine (Tegretol)

The most important action is blockade of sodium ion channels, reducing membrane excitability

Pharmacokinetics of carbamazepine:

Extensively metabolized, and one of its main metabolites is also active

Half-life falls from 35 h to 20 h over the first few weeks due to induction of its own metabolism

Can induce metabolism of other drugs e.g. steroids, theophylline, and warfarin

No i.v. preparation is available

Uses of carbamazepine

-Generalized seizures (primary or secondary)

-Partial seizures

-Trigeminal neuralgia

-Others: neuropathy (e.g. diabetic neuropathy), diabetes insipidus

Adverse effects of carbamazepine:

-CNS symptoms: (dizziness, ataxia, headache)

-Visual disturbances (blurring of vision, diplopia)

-Depression of cardiac conduction

-GI symptoms (constipation or diarrhea, anorexia)

-Skin rash (common ~10%)

-blood disorders e.g. leucopenia

-Dysfunction of liver (hepatitis, jaundice)

-kidney dysfunction (acute renal failure)

-Osteomalacia (enhanced vitamin D metabolism)

-Folate deficiency

-Reduces efficacy of contraceptive pills (enzyme induction)

2. Phenytoin

Alters ionic fluxes, mainly decreasing sodium ion fluxes in neuronal membrane (i.e. it has a membrane stabilizing effect) inhibiting the spread of seizure discharge.

Pharmacokinetics of phenytoin:

Extensively hydroxylated in the liver

This process becomes saturated (zero-order) at therapeutic concentration

Steady state concentration is reached in 2-3 days at low doses and about 2 weeks at high doses

Phenytoin is a potent inducer of hepatic metabolising enzymes, affecting its own metabolism and that of other drugs and dietary and endogenous substances such as vitamin D and folate.

It is 90% protein bound to plasma albumin

It should not be given i.m. since it precipitates in the muscles

and is poorly absorbed.

It may be given diluted as i.v. infusion slowly over one hour (the solution is alkaline and can cause thrombophlebitis).

Fosphenytoin is a pro-drug of phenytoin, soluble in water and can be given more rapidly (fewer injection site reactions).

Uses of phenytoin:

1. All forms of epilepsy except absence seizures

2. Status epilepticus

3. Other uses: cardiac arrhythmias, trigeminal neuralgia (if carbamazepine is inappropriate)

Adverse effects of phenytoin:

-CNS: impairment of cognitive functions, sedation, delirium, acute cerebellar disorder

-Rash

-Coarsening of facial features and hirsutism

-Gum hyperplasia (The catabolism of collagen is inhibited), more marked in children and in poor gum hygiene

-Teratogenicity and others ….

3. Sodium valproate (valproic acid)

Mechanism of action:

It acts by inhibiting GABA transaminase, the enzyme responsible for the breakdown of the inhibitory neurotransmitter, GABA, so increasing its concentration at GABA receptors

Extensively metabolized

Half-life ~13 h

90% bound to plasma albumin

It is non-specific enzyme inhibitor, inhibiting its own metabolism and that of other antiepileptic drugs

It is effective in:

1. All forms of epilepsy
2. Prophylaxis of migraine

Adverse effects of sodium valproate:

-Nausea, GI irritation, diarrhea

-Weight gain

-Transient loss of hair, which may grow back abnormally

-Thrombocytopenia

-Teratogenicity

-Less frequent : hepatic dysfunction, hyperactivity, ataxia, tremor, ….

-It can prolong the action of co-administered antiepileptic drugs

Other antiepileptic drugs

4. **Barbiturates e.g. phenobarbitone and primidone (a pro-drug metabolized to phenobarbitone).**

They are still used for generalized seizures.

a. Clonazepam

Clonazepam is a benzodiazepine used for treatment of all forms of epilepsy and for status epilepticus.

Effect of benzodiazepines may decrease considerably after weeks or months of continuous therapy.

b. Vigabatrin

Vigabatrin is structurally related to GABA, acts by reversibly inhibiting GABA-transaminase.

It is not metabolized and does not induce hepatic drug metabolizing enzymes

It causes visual field defect (constriction) in 30% of patients

c. Lamotrigine

Lamotrigine acts to stabilize presynaptic neuronal membrane by blocking sodium channels (similar to carbamazepine and phenytoin)

It also reduces the release of excitatory amino acids such as glutamate and aspartate

half-life is 24 h, single daily dose

Effective in all types of epilepsy including absence seizures.

May cause serious toxicity on the skin especially in children (serious rash).

Fewer sedative and cognitive effects than others

Specific unwanted effects include: insomnia and headache (not used in migraine prophylaxis)

d. Gabapentin

Gabapentin is an analogue of GABA

Excreted unchanged

Does not induce or inhibit hepatic metabolism

Used also for peripheral neuropathic pain, migraine prophylaxis and in anxiety.

e. Ethosuximide

It blocks a particular type of calcium channel that is active in absence seizures (petit mal)

Half-life is 55 h

Used specifically for petit mal epilepsy

f. Topiramate

Its mechanisms of action include blockade of sodium channels, enhancement of GABA activity, inhibition of carbonic anhydrase, … .Half-life is long (21 h, given once daily)

General Notes

-Abrupt withdrawal of antiepileptic drugs (particularly barbiturates and benzodiazepines) should be avoided

-There is increased risk of teratogenicity associated with the use of antiepileptic drugs. Increased risk of neural tube defect and other defects associated particularly with carbamazepine, phenytoin, lamotrigine, and valproate.

- ✓ Adequate supply of folate is used to counteract the risk of neural tube defect.
- ✓ First-line Drugs for tonic-clonic (grand mal) epilepsy

  Sodium valproate, Lamotrigine, Clonazepam, Carbamazepine
- ✓ First-line Drugs for absence seizures (petit mal) epilepsy

Ethosuximide, Sodium valproate (second line: lamotrigine, clonazepam)

- ✓ Drugs used in convulsive status epilepticus

  Lorazepam i.v.

  Diazepam i.v. (causes thrombophlebitis), can be given rectally

  Clonazepam, midazolam

  Phenytoin sodium i.v. slowly

  General anesthesia with thiopentone or propofol

15. Drugs For Parkinson's Disease

I. Definition

Two balanced systems are important in the control of motor activity at the level of basal ganglia. The neurotransmitter:

in one is the **acetylcholine** (excitatory)

in the other is **dopamine** (inhibitory)

In Parkinson's disease, the concentrations of dopamine are reduced (Dopamine Deficiency, mainly at D2). So that cholinergic system becomes Dominant. This results in (mainly):

- **Tremor** (at rest, diminishes with movement, absent during sleep, not necessarily in the hands)
- **Rigidity**
- **Hypokinesia**

Two approaches to restore the balance:

- Enhancing dopaminergic activity
- Reducing cholinergic activity or Both

1. **Enhancement of dopaminergic activity by different mechanisms:**
   A. **Restoring neuronal dopamine by giving levodopa** (Levodopa is the natural precursor of dopamine, dopamine is a polar compound with poor passage through GIT and BBB)
   B. **Prolonging the action of dopamine through inhibition of its metabolism:**
      - **by inhibiting the enzyme MAO-B** in basal ganglia (e.g. Selegiline: a selective and irreversible inhibitor of MAO-B) or
      - **by inhibiting the enzyme COMT** (e.g. Entacapone)
   C. **Direct stimulation of the dopamine receptors (Dopamine**

agonists)

- **Ergot derivatives**: Cabergoline (very long action)
  Pargolide
  Bromocriptine
- **Non-ergot dopamine agonists**: Ropinirole
- **Apomorphine** (a derivative of morphine with structural similarities to dopamine; it is full agonist to D1 and D2 with ergotamine-like properties).

D. Release of dopamine from stores and inhibition of its uptake (Amantadine). It is also used as antiviral drug (effective only against influenza A virus).

2- Reduction of cholinergic activity by centrally acting anticholinergic drugs (Benzhexol [trihexyphenidyl], benztropine, orphenadrine, procyclidine, …)

Dopamine Activity

Dopamine activity ⟶	Increased	Decreased
Basal ganglia	Antiparkinsonism	Parkinsonism
Medullary CTZ	Vomiting	Antiemetic
prolactin secretion (in hypothalamus)	Suppression of lactation (↓prolactin)	Galactorrhea
Cerebral cortex	Psychiatric states	Antipsychotic
Examples of drugs	Levodopa	Phenpthiazines

II. <u>Dopaminergic Drugs</u>

1. Levodopa (L-dihydroxyphenylalanine) is a natural amino acid precursor of dopamine. Dopamine is not used because:

- Poorly lipid soluble
- Not well absorbed from GIT

- Does not usefully penetrate into the CNS

Levodopa:

- Has a half-life up to 90 minutes, duration 6 hours
- Is absorbed from GIT by active transport, high doses delay gastric emptying with erratic absorption
- Is decarboxylated in the body to dopamine by peripheral and central decarboxylase enzyme
- Dopamine formed peripherally cannot pass through BBB and causes side effects: postural hypotension, arrhythmias, nausea, vomiting
- Only 1-5% of the oral levodopa dose reaches the brain (therefore, large amount of levodopa is required to be given with more side effects). **This problem is partly solved by** the use of peripheral decarboxylase inhibitors e.g. carbidopa and benserazide. They do not pass through BBB and inhibit only peripheral decarboxylation

Advantages of the combination of:

Levodopa + Carbidopa (Sinemet)

Levodopa + Benserazide (Madopar)

(Dose ratio 1 to 4) e.g. 25/100

- Same brain concentration is achieved by only 25% of the dose of levodopa given alone
- The incidence of adverse effects is less especially nausea (80% alone and 15% combination)
- The use of pyridoxine (Vitamin B6, e.g. in multivitamin preparations):
    - **can reverse** the benefit of levodopa when used alone (increased peripheral metabolism, Dopa-decarboxylase is a

Pyridoxine-dependent enzyme), but

- **cannot reverse** the effect of the combination (the enzyme already inhibited)

The use of levodopa in Parkinson's disease:

- Best effective against rigidity and hypokinesia; less effective in relieving tremor
- Start with small doses and increased gradually
- Should not be stopped abruptly
- Response after long-term therapy is gradually reduced

Adverse effects of levodopa

- Postural hypotension
- Nausea
- Levodopa-induced involuntary movement (Dyskinesias: restlessness, head movement, choreoathetosis, …) (they are dose-related)
- Cardiac arrhythmias
- Mental changes (confusion, agitation)
- The main problems of **long-term** therapy with levodopa are the **motor fluctuations**. They take the following forms:
  - Early morning akinesia
  - Peak dose dyskinesia
  - End-of-dose deterioration
  - On-off phenomenon (Patient’s response to each levodopa dose consists of swinging abruptly between violent dyskinesia during “on” and weakness and akinesia during “off”periods)

Note: Beyond the age of 70 y, the long-term complications of levodopa are milder.

Methods to avoid motor fluctuations:

- The lowest effective dose of levodopa should be used
- Avoid taking levodopa with meals
- Use small doses but more frequently
- Slow release levodopa preparation may be taken before sleep
- The use of adjunctive medications with levodopa to extend its action; such as dopamine agonists, amantadine, selegiline and COMT inhibitor

2. Bromocriptine

- Is an ergot derivative that has dopamine agonist activity (D2 agonist, weak alpha antagonist)
- Commonly used to suppress the production of prolactin
- Now rarely used for Parkinson's disease because of side effects (nausea, vomiting, postural hypotension, pleural effusion and retroperitoneal fibrosis with prolonged use – the latter side effects are that of ergot)

III. Anticholinergic Drugs

- Block acetylcholine in the CNS with less peripheral effects, partially restoring the imbalance created by a decrease in dopamine activity
- They produce improvement in tremor and rigidity more than hypokinesia
- Examples: Benzhexol (Trihexyphenidyl), benzatropine, orphenadrine, procyclidine

		Levodopa	Anticholinergic Drugs
1	Tremor	±	+ + +
2	Rigidity	+ +	+ +
3	Hypokinesia	+ + +	±

Drug-induced parkinsonism

There are drugs that can increase symptoms of parkinsonism, or induce Parkinson-like state by:

- Blocking dopamine receptors (phenothiazines, metoclopramide,…)
- Depleting dopamine stores (reserpine)
- Prolonging action of acetylcholine (anticholinesterases)

In drug-induced parkinsonism:

- Withdraw the offending drug, if possible
- Most of the cases resolve completely within 7 weeks
- An anti-muscarinic drug e.g. trihexyphenidyl is beneficial
- Levodopa and dopamine agonists are **not** useful in drug-induced parkinsonism (they may also cause psychosis)

16. Non-steroidal Anti-inflammatory Drugs

I. **Classification:**

1. salicylates as aspirin
2. Non-steroidal anti-inflammatory drugs:
   a. non-selective: ibuprofen, diclofenac sodium, indometacin, piroxicam, meloxicam, sulindac
   b. selective COX2 inhibitors: celecoxib, rofecoxib, etoricoxib
3. Paracetamol

All NSAIDs act by the same mechanism and they have three main actions including anti-inflammatory, analgesic and antipyretic.

III. Mechanism of action of NSAIDs:

They all act by inhibiting the cyclooxygenase enzyme (COX) and this inhibit the oxidation of arachidonic acid

1. Anti-inflammatory action: occurs mainly due to inhibition of prostaglandins that mediate inflammatory responses as vasodilatation, oedema, and pain. The NSAIDs suppress the pain, swelling and increased blood flow associated with inflammation, but they have little or no action on the underlying disease process. These effects mainly due to inhibition of PGE2 and prostacyclin
2. Analgesic action: NSAIDs are effective in mild to moderate pain, especially that arising from inflammation or tissue damage. This is due to decrease in prostaglandins peripherally in the inflamed tissue. They may also have a central analgesic effect possibly in the spinal cord.
3. Antipyretic action: This is due to reduction of prostaglandins production in the hypothalamus (temperature regulating center).

Bacterial toxins produce fever by releasing phylogenic substances from macrophage. NSAIDs do not affect the normal body temperature

IV. Adverse effects of NSIDs:

Prostaglandins are important in gastric cytoprotection, platelets aggregation; renal vascular auto regulation and induction of labor.

Common adverse reaction to the NSAIDs

1. gastrointestinal disturbances: are the commonest adverse effects. These occur mainly from inhibition of gastric COX-1. These include, gastric discomfort, dyspepsia, diarrhea, nausea and vomiting and gastric ulceration and bleeding. Serious haemorrhage or perforation can occur. The prostaglandin analogue misoprostol can reduce gastric damage produced by these drugs. The gastrointestinal disturbances occur less common with selective Cox-2 inhibitors.
2. Skin reactions: skin rash which is idiosynchratic is common especially with mefenamic acid and sulindac. Serious and fatal skin reaction may occur
3. Adverse renal effects: may cause reversible renal insufficiency in susceptible patients. This is due to the inhibition of prostaglandins (PGE2 and PGI2), which involved in maintenance of renal blood flow. Chronic ingestion of NSADs can cause analgesic nephropathy characterized by nephritis and renal papillary necrosis.
4. Other unwanted effects include bone marrow suppression, liver disorders, aggravation of bronchial asthma

V. Drugs

A. Aspirin and Salicylates:

1. Mechanism of action:

Aspirin (salicylic acid) and salicylates act by irreversibly inhibiting cyclooxygenase enzyme.

2. Pharmacokinetics of salicylates:

Oral salicylates are rapidly absorbed from the upper intestine and the stomach with a peak serum level occurs in 1 hour. Absorption depends on gastric pH, gastric emptying time. Following absorption, aspirin is rapidly distributed to various body tissues. Aspirin undergoes rapid hydrolysis in the body. Aspirin is 80-90% bound to plasma proteins, especially albumin. It is metabolized by the liver and then excreted by the kidneys. The half-life is dependent on the dose and range from 2-3 hours in antiplatelets dose to 12 hours in the anti-inflammatory dose.

3. **Clinical uses of salicylates:**

a. analgesic in mild to moderate pain in a dose of 300-1000 mg every 4-6 hours
b. anti-inflammatory as in arthritis in an average dose of 3-4g/day
c. cardioprotection; this is due to irreversible inhibition of platelets aggregation, usually is small doses that inhibit thromboxane but not prostacyclin
d. local effect in GIT for the treatment of ulcerative colitis as meselamine (5-aminosalicylic acid)
e. local keratolytic effect which is useful in the treatment of warts, corns and fungal infections.

4. Adverse effects:

a. GIT, nausea, vomiting, dyspepsia and peptic ulceration, which may lead to gastric bleeding. This is due to inhibition of COX1 in the gastric mucosa. The gastric effect can be reduced by the use of misoprostol or other antiulcer drugs

b. liver toxicity, especially at high doses, with increase in liver enzymes
c. effect on uric acid, low doses decrease uric acid excretion and lead to hyperuricemia, while high doses increase uric excretion, lower the blood levels and cause uricosuria
d. increase bleeding tendency due to platelets aggregation inhibition, salicylates may also potentiate the effect of anticoagulants
e. respiratory system: Salicylates increase O2 consumption and CO2 production due to uncoupling of oxidative phosphorylation, the increase CO2 stimulates respiration. Salicylates can also stimulate the respiratory centers directly
f. Reye syndrome: when aspirin given in viral infection in children was found to be associated with "Reye" syndrome which consists of hepatitis and cerebral edema and is often fatal
g. in toxic doses salicylates cause "salicylism" characterized by dizziness, tinnitus, deafness, nausea and vomiting. Salicylates in toxic doses also cause respiratory stimulation which lead to hyperventilation, hyperthermia, hyperglycemia and glucosuria.

B. Individual Non-steroidal anti-inflammatory Drugs

1. Non-Selective Cox inhibitors

a. Indometacin (indomethacin)

Is an indole derivative which is a more potent non-selective inhibitor of COX than aspirin, it also inhibits the motility of polymorphonuclear leukocytes. It has both analgesic and anti-inflammatory activities. It is estimated to be 20 times more potent than aspirin.

It is used for the closure of patent ductus arteriosus in premature infants, it is also used in ankylosing spondylitis.

High incidence of adverse effect limits its use as a long term analgesic drug . Adverse effects include GI disturbances, which can be fatal, hepatitis, pancreatitis, headache, dizziness, vertigo and mental confusion. Bone marrow suppression with neutropenia and a plastic anemia

b. Diclofenac Sodium

Diclofenac is a phenylacetic acid derivative, it is one of the most commonly used NSAID. It has analgesic anti-inflammatory and antipyretic actions. Diclofenac absorbed well when given orally with a short half-life of about 2 hours. It is metabolized by the liver.

Diclofenac is useful for the long term management of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis. It is available as tablets, injection and cream or gel for topical application.

Adverse effect mainly on the GIT, elevation of liver enzymes

c. Ibuprofen

Ibuprofen Is also a commonly used NSAID , it is a propionic acid derivative, and it is a non-selective COX inhibitor.

Absorbed rapidly when given orally and metabolized by the liver, with a half-life of about 2 hours. Used in chronic inflammatory conditions and also antipyretic as alternative to aspirin especially in children.

Adverse effects on the GIT is probably less than with aspirin, it also cause dizziness, burring of vision , skin rash

d. Naproxen

Is non-selective COX inhibitor, useful in inflammatory condition, dysmenorrhea, and acute gout. Absorbed well when given orally. Naproxen can be absorbed following rectal administration, has a variable half-life of about 14 hours, it is excreted almost entirely in the urine. It is 99% bound to plasma proteins.

e. Piroxicam

Is an oxicam derivative, a nonselective COX inhibitor and in addition, it inhibits activation of neutrophils independently, so it has an additional mechanism of action. It is well absorbed after oral administration and undergoes enterohepatic circulation. piroxicam is 90% bound to plasma proteins. Has long half-life, so can be given once daily. Is useful in osteoarthritis and rheumatoid arthritis, but less suitable for acute analgesia except for gout

f. Meloxicam

Is useful in osteoarthritis, has less gastric damage than other drugs, inhibits COX2 more than COX1

g. Sulindac

Is a derivative of indometacin, it is a pro-drug converted inside the body to sulphide, which COX inhibitor, it is about half potent as indometacin. Sulidac absorbed well when given orally metabolized by the liver into active sulphide, it is highly protein bound. It is useful in osteoarthritis, rheumatoid arthritis ankylosing spondylitis and acute gout.

Adverse effects similar to indometacin, but with lower incidence.

h. Ketorolac

Is a potent analgesic, but has moderate anti-inflammatory effects. Its use is limited to the short term(5 days) treatment of pain as it can be given im, iv and orally. It has a rapid onset and a short duration of action. It is useful in postoperative pain. Topical ophthalmic form is useful in the treatment of allergic conjunctivitis.

Adverse effects include, GIT, dyspepsia, nausea, vomiting and gastric bleeding, also headache and dizziness.

i. **Mefenamic acid**

is a non-selective COX- inhibitors useful in the treatment of osteoarthritis, rheumatoid arthritis, postoperative pain dysmenorrhea and menorrhagia
Adverse effects include GI disturbances, skin rash, fatigue, hypotension and palpitation, glucose intolerance, hemolytic anemia and thrombocytopenia

2. Selective COX-2 inhibitors

These include the cyclic coxibs as celecoxib, etoricoxib, rofecoxib, parecoxib and lumeracoxib
They have high affinity for COX-2 than COX-1, they are effective in relieving pain and having anti-inflammatory effect, they have no effect on platelets aggregation

a. **Celecoxib**

Is selective reversible inhibitor of COX-2 enzyme, it does not inhibit platelets aggregation.
It is readily absorbed from the GIT with peak serum level in about 3 hours. Celecoxib is extensively metabolized by the liver and excreted in the urine and feces. The half-lifer is about 11 hours, and usually taken once daily. It is useful in osteoarthritis, rheumatoid arthritis, primary dysmenorrheal and pain relief .
Adverse effects include abdominal pain, diarrhea and dyspepsia with less incidence of peptic ulcer. It is contraindicated in patients allergic to sulphonamides. Kidney damage may occur and the drug should be avoided in patients with renal insufficiency. Celecoxib was found to increase the risk of myocardial infarction and stroke related to dose and underlying risk factors. The drug should be avoided in patients at risk of cardiovascular or cerebrovascular disease.

b. Parecoxib

Is selective COX-2 inhibitor which can be given by injection, it effective analgesic for the relief of moderate to severe postoperative pain.
Its rapidly (5 minutes) absorbed following intramuscular injection and converted to valdecoxib , the active metabolite of the drug. Valdecoxib is metabolized by the liver.

c. Etoricoxib

Is COX-2 selective. It is incompletely absorbed following oral administration with a half-life of about 20-26 hours. It is extensively metabolized by the liver and the dose needs to be adjusted in liver disease. Used in a single daily dose for the treatment of osteoarthritis, rheumatoid arthritis and gouty arthritis. Etoricoxib is also useful in dysmenorrhea and post-operative pain. Etoricoxib has less incidence of GIT adverse effect but can increase the incidence of stroke and myocardial infarction.

3. Paracetamol

Paracetamol (acetaminophine) has little or no anti-inflammatory activity

Mechanism of action

Paracetamol inhibits prostaglandins synthesis centrally in the brain. This explains its antipyretic and analgesic effects. Paracetamol has less effect on cyclooxygenase in the peripheral tissue, which explains its weak anti-inflammatory activity. Paracetamol also has no effect on platelets function.

Pharmacokinetics

Paracetamol is rapidly absorbed from the GIT. It undergoes first pass metabolism by the liver. Paracetamol is conjugated with glucuronide and sulfate the liver. A portion of paracetamol is hydroxylated to form N-acetylbenzoiminoquinone (NAPQI), which is highly reactive and toxic

metabolite that can combine with the SH- group . At normal dose the toxic metabolite is combines with the SH- group of glutathione.

Clinical uses

Paracetamol is used as analgesic and antipyretic especially in patients with peptic ulcer or gastritis. It also has no effect of platelets function and no interaction with anticoagulant drugs.

It is also the antipyretic of choice in children with viral infection or chicken pox (aspirin may cause "Reyes" syndrome in children with viral infections).

Also paracetamol has no effect on uric acid excretion and can be used safely in patients with gout

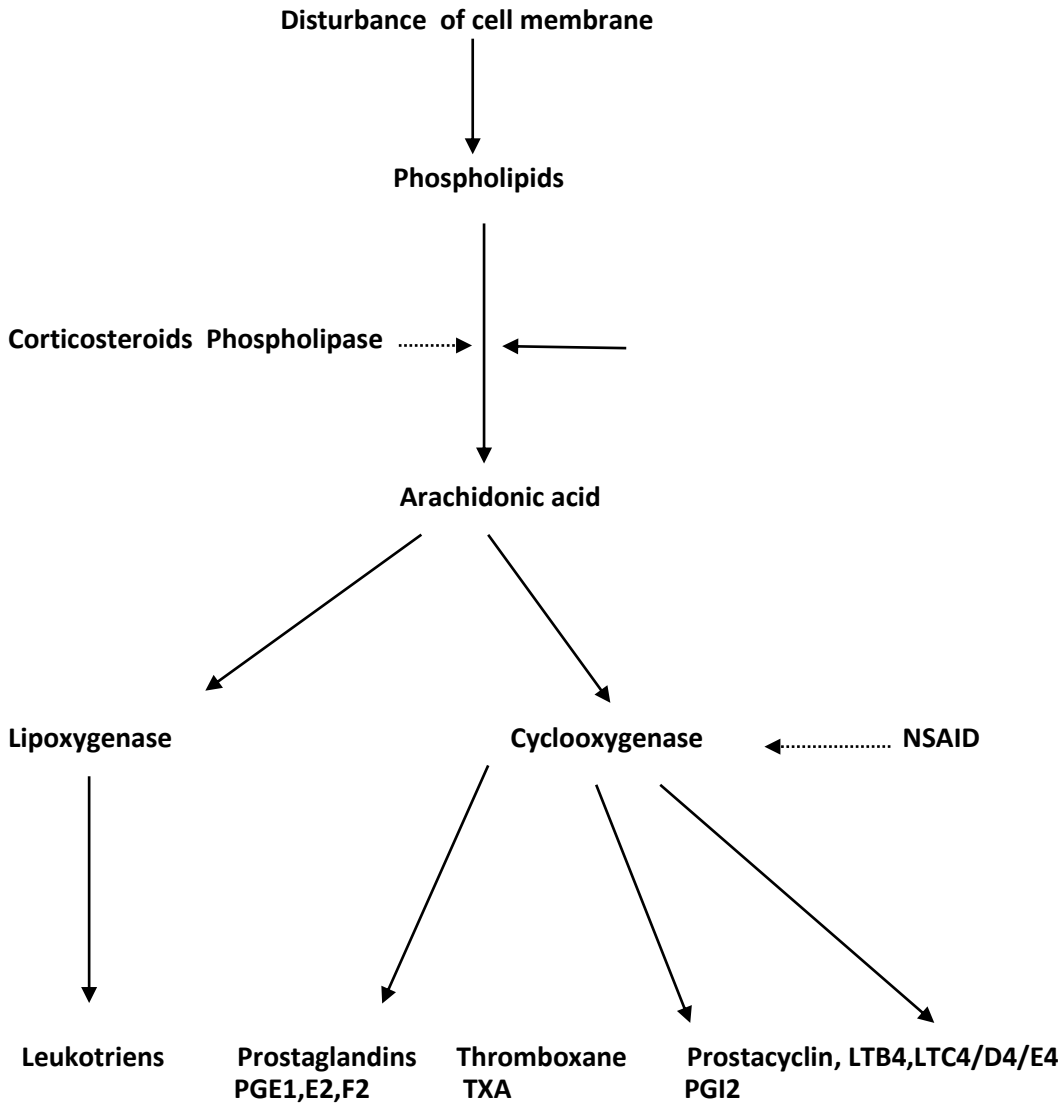
Adverse effects

Paracetamol in normal therapeutic doses it is free of side effects, very rarely it causes skin rash and minor allergic reactions

Paracetamol overdose

Acute ingestion of paracetamol in high doses (> 7.5g) can result in toxicity. The main toxicity includes hepatic necrosis, renal tubular necrosis, hypoglycemia and coma. The toxicity results from the accumulation of NAPQI which binds to macromolecules of the liver cells, this lead to enzyme inactivation and damage of the liver cells. Doses of 20-25 g are potentially toxic due to acute liver failure.

The antidote for paracetamol toxicity is N-acetylcysteine which is a precursor of glutathione that help the inactivation of NAPI and reduce its toxicity


Disturbance of cell membrane
Phospholipids
Corticosteroids Phospholipase
Arachidonic acid
Lipoxygenase
Cyclooxygenase
NSAID
Leukotriens
Prostaglandins PGE1,E2,F2
Thromboxane TXA
Prostacyclin, LTB4,LTC4/D4/E4 PGI2

17. Narcotic Analgesics

I. Overview: Two terms need to be clarified: **Opioids**: a term applies to natural or synthetic substance which produce morphine-like effect that are blocked by naloxone (morphine antagonist); **Opiate**: is a term restricted to drugs such as morphine and codeine obtained from the opium poppy

Opium:

Is an extract of the juice of the ***poppy papaver somniferum***. Opium is known for thousands of years as an agent which produces euphoria, analgesia, sleep, and to prevent diarrhea.

II. Classification

Opioid (Morphine and morphine-like drugs) are classified according to their effects on the receptors into the following classes:

Strong Agonists	Moderate Agonists	Mixed agonist-antagonist	Antagonist	Other analgesic
Morphine Pethidine Methadone Heroin Fentanyl	Codeine Propoxyphene	Pentazocine nalorphine Buprenorphine	Naloxone	Tramadol

Modified from Lippincott's illustrated reviews: pharmacology, 5th edition 2012.

Opioid receptors

Various pharmacological actions produced by morphine implied that there is more than one receptor involved in these effects. There are three types of receptors recognized in the effect of morphine. These are:

Functional effects associated with the main types of opioid recept			
	μ (Mu)	δ (Delta)	κ (Kappa)
Analgesia			
Supra-spinal	+++	-	-
Spinal	++	++	+
Peripheral	++	-	++
Respiratory depression	+++	++	-
Pupil constriction	++	-	+
Reduced GI motility	++	++	+
Euphoria	+++	-	-
Dysphoria	-	-	+++
Sedation	++	-	++
Physical dependence	+++	-	+

III. Mechanism of action of opioid:

Effect of opioid on various receptors results in:

1. Inhibition of adenylate cyclase which results in reducing intracellular cAMP.
2. Opening of K^+ (potassium) channels
3. Inhibition of opening of voltage-gated calcium channels.

These effects reduce both:

a. Neuronal excitability (because increased K^+ conductance causes hyper polarization of membrane)

b. Transmitter release (due to inhibition of calcium entry)

Effects on the nociceptive pathway:

Centrally, opioid receptors are widely distributed in the brain. For the analgesic action of morphine 5-HT pathways is involved.

At the spinal level, morphine inhibits transmission of nociceptive impulses through the dorsal horn and suppresses nociceptive spinal reflexes, even in patients with spinal cord transection

At peripheral level, there is also evidence (see Rang and Dale 2006) that opiates inhibit the discharge of nociceptive afferent terminals in the periphery, particularly when inflammation exists. Injection of morphine into the knee joint following surgery to the joint provides effective analgesia. This means that opioid analgesia is not exclusively a central phenomenon.

IV. Pharmacological actions:

1. Effects on the central nervous system:
    a. Analgesic
    b. Euphoria: is mediated through μ (Mu) receptors and is balanced by dysphoria produced by the effect on (Kappa)-receptors.
    c. Respiratory depression: this is also mediated through the (Mu) receptors. Respiratory depression is caused by reduction of the sensitivity of respiratory center to carbon dioxide. Respiratory depression is the commonest cause of death in opioid poisoning.
    d. Depression of cough reflexes: suppression of cough seems not correlated with analgesic effect; for example, codeine suppresses cough at sub-analgesic doses.
    e. Nausea and vomiting: these occur in up to 40% of patients to whom morphine is given. This seems to be due to stimulation of chemoreceptor trigger zone.

f. Pupillary constriction: this is centrally mediated, caused by the (μ)(Mu)-and (k)(kappa)- receptors stimulation. Pinpoint pupil is an important diagnostic feature of morphine overdose.

2. Effects on gastro-intestinal tract.

   Morphine increases tone and reduces motility in many parts of the GIT resulting in constipation. Morphine also results in contraction of the gall bladder and results also in constriction of the biliary sphincter.

   This effect is harmful in patients suffering from biliary colic due to gall stones.

3. Other actions of opioid:

   Morphine releases histamine from mast cells by an action not related to opioid receptors. Release of histamine may cause urticaria and itching at the site of injection. Bronchoconstriction is also recognized with morphine treatment which is due to histamine release? Morphine is dangerous in asthmatic patients.

   Hypotension is also noticed in morphine treated patients as a result of vasodilatation caused by histamine release and also as a result of an action on the medulla.

V. Pharmacokinetic of morphine and morphine analogues:

Morphine is slowly absorbed and is commonly given by IV or IM routes. Codeine is well absorbed from the GIT. The half-life of morphine is 3-6 hours, and the liver is the main site of metabolism usually by conjugation with glucouronides. Morphine is being reabsorbed (Entero-hepatic circulation). **Diamorphine** and **codeine** are metabolized in the body to morphine.

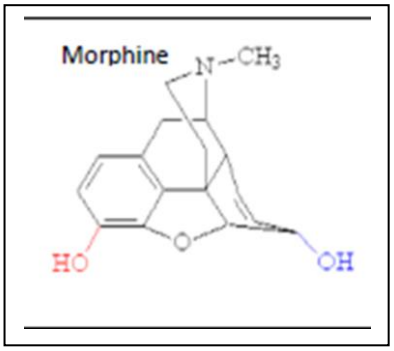
VI. Side effects of opioid:

Nausea and vomiting

Constipation

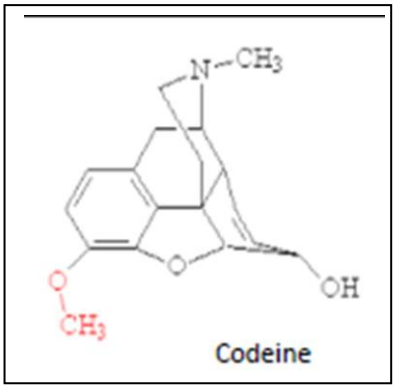
Drowsiness

Respiratory depression and hypotension.

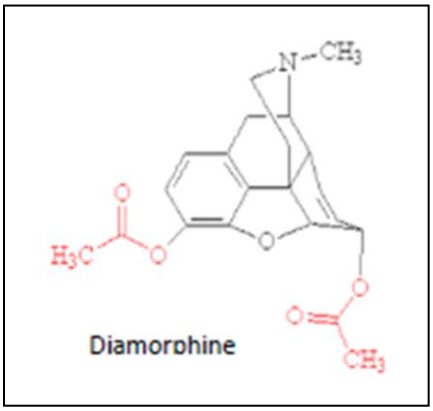


VII. Choice of drugs:

1. Morphine: is the most commonly used analgesic for severe pain. It frequently causes nausea and vomiting.

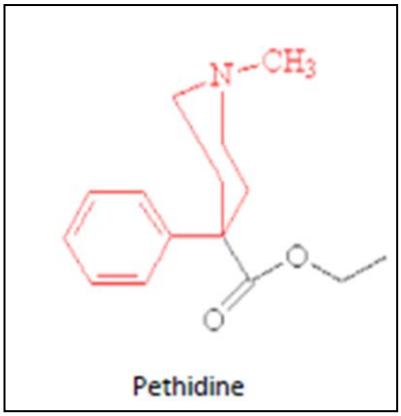


2. Codeine: is effective for the relief of mild to moderate pain. Unlike morphine, it causes little or no euphoria and is rarely addictive. Codeine produces respiratory depression similar to morphine, however, this is rarely a problem in clinical use. The main use of codeine is in treatment of cough (anti-tussive).
3. Diphenoxylate: This is a widely used drug for treatment of diarrhea. It is present in combination with a small dose of atropine (Lomotil, or enterostop). Atropine toxicity in this combination is used to limit abuse of the drug.
4. Dextropropoxyphen: has little analgesic effect (similar to codeine). It is usually given in combination with paracetamol.



5. Diamorphine (**heroin**): it is diacetylmorphine (the letter ‘a’ after the ‘Di’ is for acetyl. it is a powerful analgesic. It may cause less nausea and hypotension.
6. Pethidine (it is called meperidine): The pharmacologic effect of pethidine is very similar to morphine but

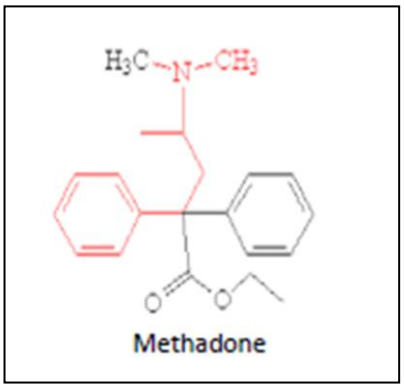
there are substantial differences:



Pethidine

- it causes restlessness rather than sedation.
- Pethidine has antimuscarinic effect which may cause dry mouth.
- It causes euphoria and is liable for dependence.
- Pethidine is preferable to morphine for analgesia during labour because it is short acting.
- A significant drug interaction is reported with monoamine oxidase inhibitors. This is manifested as excitement, hyperthermia, and convulsion. The underlying mechanism of interaction is not fully explored but possibly due to increased formation of norpethidine metabolites

7. Fentanyl and Alfentanil: these drugs are used for intra-operative analgesia.
8. Methadone: it is less sedating than morphine and the duration of action is longer than morphine.
   For this reason, methadone is widely used in the treatment of morphine and diamorphine addiction.



Methadone

9. Pentazocine: is a mixed agonist-antagonist. It has agonist activity on Kappa-receptors and antagonist activity on Mu- receptors. Its potency is similar to morphine but less respiratory depressant than morphine. It causes **dysphoria** rather than euphoria. It tends to **raise blood pressure** rather than to decrease it. Because it has antagonistic activity it antagonizes various effects of morphine such as analgesic effect when given in the same time.

10. **Tramadol** is an opioid with additional actions; the basis of its analgesic effects are due to a combination of:
    - **a.** relatively weak agonist action on μ –receptors.
    - **b.** inhibition of neuronal noradrenaline uptake resulting in increased CNS noradrenaline.
    - **c.** enhanced serotonin release.

    It is rapidly absorbed from the gastrointestinal tract, 20% of an oral dose undergoes first-pass metabolism and less than 30% of the dose is excreted unchanged in the urine ($t_{1/2}$ 6 h). Tramadol is approximately as effective as pethidine in reducing pain. Tramadol is claimed to be less likely to cause constipation, depression of respiration and less addicting liability. Confusion, convulsions, hallucinations and anaphylaxis have been reported with its use. (taken from Laurence, clinical pharmacology, 2003).
11. Naloxone: it is pure opioid antagonist for the three opioid receptors (μ, Delta, and kappa-receptors). It antagonizes morphine effects. Naloxone has no effect on pain threshold. The main clinical use of naloxone is to treat respiratory depression caused by opioid overdose. Naloxone has no important unwanted effects but precipitate withdrawal symptoms in addicts. It can be used to detect opioid addicts.

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18. Drugs for gout

Learning objectives

1. Pathophysiology of gout
2. Drugs that precipitate gout
3. Drugs used for acute gout
4. Colchicine in acute attack of gout
5. Management of chronic gout
6. Probenecid and the uricosuric agents.

A. Drugs for Gout: Definition

Gout is a metabolic disease characterized by hyperuricemia & episodes of recurrent acute arthritis due to deposition of urate in joints & cartilage (especially of big toe).

Hyperuricemia & gout depend on two processes:

1. Overproduction of uric acid
2. Under excretion of uric acid

B. Pathophysiology

The inflammatory process is infiltration of leukocytes inside the synovial cavity, these cells phagocytize urate crystals & then breakdown causing release of destructive lysosomal enzymes, PGs & IL-1.

When hyperuricemia is chronic, large & gritty deposits (known as tophi) may form in affected joints; deposition of urate crystals in kidney causes renal damage.

C. Drugs that precipitate gout

1. Overproduction of urate- due to excessive cell destruction releasing nucleic acids, occurs when myeloproliferative or lymphoproliferative disorders are treated by drugs.
2. Under excretion of urate- is caused by:

a. Thiazide & loop diuretics
b. Low doses of aspirin
c. Ethambutol & pyrazinamide
d. Nicotinic acid, ciclosporin
e. Alcohol- increases urate synthesis & also causes a rise in blood lactic acid that inhibits tubular secretion of urate.
f. Food also precipitate gout especially those with excess purines (red meat, sea food, legumes)

Drugs that have a mild uricosuric effect & increase renal clearance of urate are losartan & fenofibrate.

D. Drug management:

1. To relieve acute gouty attacks (anti-inflammatory drugs e.g. indometacin, diclofenac, naproxen, piroxicam) or colchicine or oral corticosteroids
2. To prevent urate synthesis e.g. allopurinol, febuxostat
3. To promote urate elimination (uricosuric drugs) e.g. probenecid, sulphinpyrazone

I. Treatment of acute gout

1. NSAIDs are highly effective, terminating attack in few hours; early treatment is important.

- Indometacin is first choice orally; naproxen, diclofenac, piroxicam & etoricoxib are effective alternatives.
- Aspirin is not used because low doses cause urate retention

2. Colchicine is an alternative when NSAIDs are contraindicated.

It is anti-inflammatory drug specific for gout, it is an alkaloid from autumn crocus (*Colchicum autumnale*)

a. **Mechanism of action**

Is not well understood but relates to its effects on neutrophils (which play a prominent role in the pathology of gout). It inhibits the assembly of microtubules, thus interfering with mitotic spindle formation and arresting cell division as well as inhibiting cell migration.

It rapidly relieves pain & inflammation most effectively if used within 24h of onset of acute attack; inflammation disappears completely within 2-3 days. This swift effect confirms diagnosis because non gouty arthritis is unaffected, though failure doesn't prove the patient is free of gout.

b. **Pharmacokinetics**

is absorbed from gut, concentrated in kidney, spleen, liver & GIT, some metabolized in liver & some excreted unchanged in bile & reabsorbed from gut, this enhances gut toxicity. Majority is excreted in feces, 15-30%in urine

c. **Side effects**

Abdominal pain, nausea, vomiting, the most common is diarrhea (may be bloody) due to inhibition of mitosis in rapidly proliferating cells of intestinal mucosa (this usually responds to reduction of dose)

Rarely causes hair loss, bone marrow depression, peripheral neuritis & myopathy

*iv colchicine causes less GIT toxicity

II. Management of chronic gout

1. Treatment of risk factors for hyperuricemia which include:
   a. Obesity
   b. Hypertension
   c. excessive alcohol intake

d. high dietary intake of purines

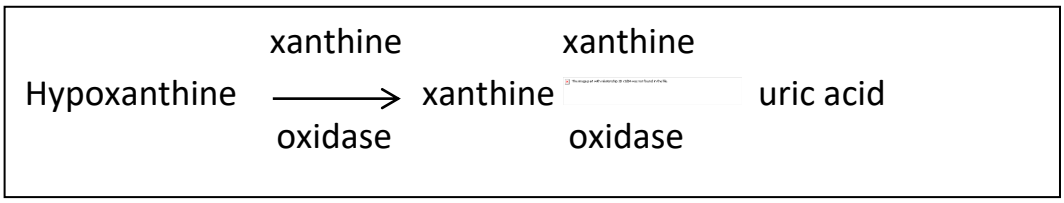
- Attention to these factors will prevent further attacks
- Rapid lowering of plasma uric acid by any means may precipitate acute gout, probably by causing dissolution of tophi. Thus a NSAID or colchicine must be prescribed concomitantly for first 6 months with uric acid reducing medication, or NSAIDs for 6 weeks.

2. Drugs for chronic treatment of gout

A. Prevention of uric acid synthesis

1. Allopurinol (Zyloric)

   It inhibits xanthine oxidase (enzyme that converts xanthine & hypoxanthine to uric acid)



Uses

a. recurrent gout

b. prevents hyperuricemia due to diuretics

c. can be combined with uricosuric agent

d. during treatment of myeloproliferative disorders when cell destruction creates a high urate load

Side effects

Precipitation of acute gout, allergic reactions (Allopurinol hypersensitivity syndrome) are uncommon but may be severe (exfoliative rash, arthralgia, fever, lymphadenopathy, vasculitis & hepatitis); deaths have been reported

Drug interactions

a. is enzyme inhibitor, inhibits metabolism of probenecid, oral anticoagulants & increases hepatic iron concentration

b. allopurinol with ampicillin, increase the incidence of rash , so allopurinol should be discontinued immediately

2. Febuxostat (Adenuric, Uloric)

Is a selective xanthine oxidase inhibitor, licensed in Europe in 2008 & in USA in 2009, is recommended for patients who are intolerant to allopurinol.

3. Uricosuric drugs

a. Probenecid (benemid)

It inhibits urate reabsorption & increases its excretion in urine

Pharmacokinetics is rapidly absorbed after oral administration, is highly protein bound.

*High fluid intake should be taken to prevent dangers of mechanical obstruction or stone formation

Side effects GIT upset, allergy, drowsiness, renal injury from deposition of urate in kidneys

Contraindications 1. severe renal impairment

2. patients with renal calculi

Drug interactions

It prolongs effect of organic acids e.g. penicillin, indometacin, cephalosporins, so the dose of these drugs should be adjusted.

4. Sulfinpyrazone (a metabolite of phenylbutazone)

Acts like probenecid, it lacks analgesic & anti-inflammatory actions, so is useless in acute gout.

It is a potent uricosuric, alkalinization of urine & high fluid intake is necessary to prevent crystalluria

Side effects gastric upset, risk of uric acid deposition in kidney

- It is contraindicated in active peptic ulcer
- Prolonged use of allopurinol & uricosuric agents can decrease size of tophi & even removed.

19. Drug treatment of rheumatoid arthritis

Learning objectives

1. Aim of drug therapy
2. Use of non-steroidal anti-inflammatory drugs (NSAIDs)
3. Disease modifying anti-rheumatic drugs (DMARDs) and pharmacological details
4. Role of corticosteroids in rheumatoid arthritis
5. Use of anti-TNFα agents

A. Definition: Rheumatoid arthritis is a systemic autoimmune inflammatory disorder that is characterized by inflammation within synovial joints, causing pain, swelling and stiffness, it may progress to erosion and eventually to joint destruction.

Drug therapy is used:

1. To relieve pain, inflammation & muscle stiffness with NSAIDs
2. To modify course of disease or induce remission

B. Drugs

1. NSAIDs are drugs of first choice in rheumatoid arthritis, they relieve symptoms but not slow disease progression.

NSAID (with pronounced anti-inflammatory effect and more risk of adverse effects) is needed.

e.g. aspirin (2-6g/day)

indometacin may be used orally or as suppository the night before to relieve nocturnal pain or morning stiffness because of long duration of action. Piroxicam is also used

- Gastric intolerance & PU may be reduced by concomitant use of H_2 antagonists or misoprostol, or using selective COX-2 inhibitors.

2. Disease modifying anti-rheumatic drugs (DMARDs)

Are agents that reduce disease activity & prevent radiologically determined disease progression. They require 4-6 months of treatment for a full response.

- They decrease ESR, C-reactive protein & RF (rheumatoid factor) titer.

a. Methotrexate (Rheumatrex)

Is used as first line treatment in rheumatoid arthritis in 60% of patients at lower doses than those needed in cancer chemotherapy.

Mechanism of action It inhibits folate-dependent enzymes involved in purine biosynthesis, thus reducing lymphocyte proliferation. In recent years, it is thought that it inhibits 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, this will lead to increase the amount of AICAR that inhibits the degradation of adenosine. The increased plasma concentrations of adenosine, is thought to mediate many anti-inflammatory effects like TNFα production.

- It is the most rapid acting disease modifying drug, its therapeutic effect develops in 3-6 weeks, $t_{1/2}$=6-9h, is given orally once weekly & gradually increase the dose as bone marrow & liver function allows. Parenteral administration is possible, but is mainly used in pediatrics.
- It is excreted mainly in urine & 30% in bile

Clinical uses

1. rheumatoid arthritis
2. as a cytotoxic drug (in high doses)

3. psoriatic arthritis
4. less commonly in connective tissue diseases like SLE

Adverse effects The most serious side effects are bone marrow toxicity, hepatic toxicity and pneumonitis.

Regular (at least monthly) monitoring of full blood count and liver function test are recommended.

Mouth ulcers and nausea are common and can be improved by co-administration of folic acid (5mg).

Contraindications

1. Moderate to severe renal impairment
2. Liver disease
3. Pregnancy because it is embryotoxic (both male & female patients should avoid conception for at least 6 months after cessation of methotrexate)
4. Breast feeding
5. Active infection

b. **Sulfasalazine** is a conjugate of mesalazine (5-aminosalicylic acid) coupled to sulfapyridine.

- It is poorly absorbed from gut but is cleaved by bacterial azoreductases in colon to release mesalazine & sulfapyridine.
- Mesalazine i. inhibits both COX & lipo-oxygenase enzymes
  ii. scavenge free radicals
  iii. inhibits production of pro-inflammatory cytokines & immunoglobulins
- Sulfapyridine component is the active moiety in rheumatoid arthritis, it reduces rheumatoid factor titers, inhibits IL-2 induced T-cell proliferation.

Adverse effects nausea, vomiting, headache & rash (common), hemolytic anemia , methemoglobinemia & SLE like syndrome(rare), it causes reversible infertility in male & not in female & is not teratogenic.

c. Leflunomide

It inhibits dihydro-orotate dehydrogenase, a mitochondrial enzyme required for synthesis of pyrimidines. It arrests proliferation of activated T-cells.

It is licensed for treatment of rheumatoid arthritis and psoriatic arthritis.

Adverse effects diarrhea is the commonest, allergic reactions, alopecia, hypertension, leucopenia and hepatitis.

d. Gold salts

Its use is decreased as a result of its toxicity & increased use of methotrexate & more recently anti-TNFα biological agents

e.g. Sodium aurothiomalate by deep i.m. injection.

Auranofin orally, is less effective but has less severe adverse effects

Adverse effects

Mouth ulcers, irreversible skin pigmentation, proteinurea, blood dyscrasias, hepatitis, peripheral neuropathy and pulmonary fibrosis.

Contraindications hepatic & renal disease, pregnancy & lactation.

e. Hydroxychloroquine (antimalarial drug)

Is used as an adjunct to other disease modifying drugs. The mechanism of action is unclear but in vitro found to reduce production of pro-inflammatory cytokines including TNFα & IL-β. It is best to be used in mild disease. It is relatively nontoxic.

Adverse effects

It is well tolerated, low incidence of side effects like GIT disturbances & rashes. Retinal toxicity rarely occurs with long term use.

Cautions & contraindications

Hepatic & renal impairment, G6PD deficiency, breast feeding.

3. Adrenal corticosteroids

They may be considered as DMARD because they reduce disease severity & associated damage but its clinical effects are noticeable within 24h.

- Is usually given orally (Prednisone & Prednisolone)

Steroids are used for the following conditions:

1. To provide in-term relief of inflammatory symptoms during weeks that is taken by DMARDs
2. In severe cases like vasculitis or rheumatoid lung
3. During failure of DMARDs or development of intolerable side effects
4. Intra-articular injection of steroids when one or two joints are involved

4. Other immunosuppressants

- Azathioprine, ciclosporin, cyclophosphamide, are used in resistant cases
- Interference with cytokine expression or signaling

  Cytokines play a central role in immune response & in rheumatoid arthritis, TNF-α appears to be at the heart of inflammatory process.

  Anti-TNFα agents include:

  1. Infliximab is humanized monoclonal IgG1 Abs, causes down regulation of macrophages & T-cell function, given with methotrexate by iv infusion.
  2. Etanercept is a recombinant molecule, is licensed to be used s.c. in rheumatoid arthritis in adults.

20. Drug treatment of headache : Treatment of migraine

Definition

Headache could be:

- Primary e.g. migraine
- Secondary e.g. headache attributed to disorders of cranium, neck, eyes, ear, nose, sinuses, teeth, mouth, psychiatric problems…etc

  Migraine is a primary episodic headache disorder characterized by various combinations of neurological, GI and autonomic changes

Four phases of migraine attack:

(common but not necessarily experienced by all migraine sufferers)

1. The prodromal phase (occurs hours or days before the headache, altered mood, irritability, fatigue, yawning, ….)
2. The aura (immediately precedes the headache, visual e.g. flashes, zigzag lines, blurred vision…, paresthesias, ….)
3. The headache phase
4. The postdrome phase (Tiredness, malaise, weakness, …..)

The headache phase

The typical migraine headache is unilateral and throbbing, aggravated by physical activity. The pain may be bilateral. Onset is gradual

Usually lasts 4-72 hours

Frequency is variable (average 1-3 attacks per month)

Nausea occurs in 90%, vomiting in one third of patients

Photophobia, …. etc

Pathophysiology is complex

A phenomenon called: cortical spreading depression

The neurological activity is depressed in an area of the cortex resulting in release of inflammatory mediators (such as serotonin, substance P,…) from the sensory nerve ending in the brain.

Migraines may begin when blood vessels in the brain contract and expand inappropriately, starting in the occipital lobe.

Reduced blood flow triggers the aura. Then, blood vessels dilate causing throbbing headache. Serotonin is implicated in its pathogenesis.

Triptans activate serotonin receptors to stop migraine attack

I. Management of migraine

Three areas

1. Avoidance of triggering factors
2. Symptomatic treatment of acute attack (Abortive therapy: more effective if given early)
3. Prophylactic (preventive) therapy

Triggering Factors

Stress, Certain foods (chocolate, cheese, ice cream)

Bright lights, Loud noises, Hormonal changes, hypoglycemia

II. Drugs Used For Acute Attack (Abortive)

A. Non-specific Drugs

The first line of treatment:

- Analgesics (paracetamol or NSAIDs e.g. aspirin, ibuprofen, naproxen, tolfenamic acid)
- Caffeine, Metoclopramide or Domperidone are usually used with the analgesic drugs

B. Specific Drugs: Triptans and Ergots

During migraine attack, emptying of the stomach is slowed, resulting in

nausea and a delay in absorption of drugs. Caffeine can partially reverse this effect.

Metoclopramide and domperidone are motility stimulants (increase gastric emptying and increase absorption of analgesic drugs) and also act as antiemetics; preventing nausea and vomiting.

The earlier these drugs are taken in the attack, the better their effect

Codeine and opioid-containing compounds have limited efficacy and are better avoided.

Antiemetics are better used before analgesic drugs. Intravenous metoclopramide is more effective than oral in severe cases

1. Triptans (Selective 5-HT1 agonists)

They are effective first line treatment for moderate to severe headache or after failure of analgesics. They are used if there are no cardiovascular contraindications.

Sumatriptan

Selectively stimulates a subtype of 5-HT1 receptors (1B/1D) that exists in cranial blood vessels causing them to constrict

Rapid oral absorption

Extensive first pass metabolism

For rapid response, it can be given subcutaneously

If the first dose of a triptan is not effective, a second dose unnecessary

Adverse reactions of sumatriptan

malaise, fatigue

Sedation, vertigo

Nausea and vomiting after oral use

Feeling of chest pressure and pain due to coronary artery spasm (in 5%)

Contraindicated in patients with ischemic heart disease, and previous MI

Eletriptan is probably the most effective in the triptan class

2. Ergotamine

No longer a first-line therapy because of difficulties in absorption and adverse reactions (nausea, vomiting, abdominal pain and muscular cramps, peripheral vasoconstriction from ergotamine can persist for as long as 24 hours and repeated doses lead to cumulative effect

Dose limit: e.g. 1-2mg at the onset, 4mg in 24 hours, not to be repeated at intervals of less than 4 days, maximum 8mg in one week.

Ergotamine may precipitate angina

It should not be used for prophylaxis

Its GI absorption is poor (rectal route may be preferred in acute attack)

It is extensively metabolized in liver (contraindicated in liver disease)

3. Prophylactic Therapy

- *Beta blockers (particularly metoprolol and propranolol)*
- *Serotonin antagonists e.g. pizotifen, cyproheptadine*
- *Anticonvulsants e.g. sodium valproate, topiramate*
- *NSAIDs*
- *Antidepressants especially amitriptyline*
- *Calcium channel antagonists*
- *Others: clonidine, methysergide*
- Methysergide is a semi-synthetic ergot alkaloid; has a dangerous side effect (retroperitoneal fibrosis)
- Pizotifen

  Is an antihistamine with serotonin antagonistic activity

  Structurally related to tricyclics

Has antimuscarinic effects

As antihistamine, produces drowsiness

Also causes weight gain

21. General Anesthetics

I. Historical Events

1842 Ether administration for dental extract

1844 Nitrous oxide for dental extraction

1846 First surgical operation under ether anesthesia in England

II. Phases of the general anesthesia

The general anesthetic process extends:

- Before surgery (pre-anesthetic medication)
- During Surgery
- After surgery

A. Before surgery (pre-anesthetic medication)

The aim is to produce one or more of the following:

a. drying of bronchial and salivary secretions

b. prevention of pulmonary aspiration of gastric contents

c. anxiolytic and amnesia

A lot of adrenaline is secreted making the patient more liable to cardiac

arrhythmias. Benzodiazepines may be used for this purpose

a. Analgesia is given if the patient is in pain or to prevent postoperative pain

- Parenteral opioid such as morphine can be given for severe pain
- Paracetamol can be given to prevent postoperative pain
- NSAIDs can be used with caution (they may prolong bleeding time and may cause intra or post-operative bleeding)

b. Drying of bronchial and salivary secretions by antimuscarinic drugs.
They are rarely used e.g. may be used with bronchoscopy

c. Prevention of pulmonary aspiration of gastric content.
Patients at risk are those with full stomach, in the third trimester, or with incompetent gastro-esophageal sphincter
Aspiration or its effect can be prevented by a single dose of one or more of the following:

- antacids
- H2-blockers
- proton pump inhibitors
Metoclopramide (which hastens gastric emptying and increases the tone of the lower esophageal sphincter; it is also an antiemetic)

B. During Surgery

The aim is to induce:

- Unconsciousness
- Analgesia
- muscle relaxation

A typical general anesthetic procedure consists of:

a. Induction of anesthesia
b. Maintenance of anesthesia

a. Induction of anesthesia

1. usually by intravenous anesthetics
(propofol, thiopental, etomidate, ketamine)
2. less commonly, induction is achieved by inhalational anesthetics
(usually used in children, for example, with sevoflurane)

b. Maintenance of anesthesia

is achieved by using oxygen with nitrous oxide, or with a volatile agent (e.g. sevoflurane or isoflurane) plus additional doses of neuromuscular blocker or an opioid as required.

C. After surgery

Relief of pain: using parenteral morphine, oral or rectal paracetamol or an NSAID. Paracetamol and NSAIDs can also be given by injection.

Postoperative nausea and vomiting:

- Cyclizine, metoclopramide or ondansetron can be used.
- Dexamethasone also reduces incidence of postoperative nausea and vomiting.
- Combination of these drugs can be more effective in severe cases.

Some Special Anesthetic Techniques

Dissociative anesthesia is a state of profound analgesia and anterograde amnesia with minimal hypnosis during which the eyes remain open (the patient feels dissociated from his environment in a trance-like state). This type can be produced by ketamine. It is useful if modern equipment are lacking.

1. Sedation and amnesia without analgesia

   Provided by i.v. benzodiazepines (e.g. midazolam or diazepam) used alone for procedures causing mild discomfort e.g. endoscopy and with local anesthetic for removal of impacted wisdom tooth. The patient remains cooperative.

   Benzodiazepines can cause respiratory depression and apnea especially in elderly or in patients with respiratory insufficiency.

Combination of an opioid and a benzodiazepine is particularly dangerous.

III. General Anesthetics

Mode of action of general anesthetics

General anesthetics act on the brain primarily on the midbrain reticular activating system (hypnosis and amnesia) and the spinal cord (inhibiting motor response to painful stimuli).

They interact with proteins to alter the activity of specific ion channels.

In general, the more lipid soluble the general anesthetic, the more anesthetic effect it has.

A. Inhalational anesthetics

The preferred inhalational anesthetics are: minimally irritant and non- flammable. Examples: nitrous oxide and fluorinated hydrocarbons such as isoflurane.

An inhalational anesthetics with high blood solubility has low brain entrance and provides slow induction.

Low blood solubility → High brain entrance → Rapid induction

e.g. nitrous oxide and sevoflurane have low blood solubility and provide rapid induction.

After discontinuation of the inhalational anesthetics, the drug flows from the blood to the alveoli which significantly lower the alveolar oxygen concentration. This is called diffusion hypoxia and it is prominent with gases of low solubility in blood, having rapid diffusion rate.

1. **Nitrous oxide (1844)**

- Sweetish smell
- Non-flammable
- Non-explosive
- Provide light anesthesia without depression of respiration or vasomotor center if oxygen tension is normal.

Advantages of nitrous oxide

- Has a strong analgesic action
  50% of N2O in 50% oxygen (Entonox) has similar analgesic effect as morphine.
- Induction is rapid
- Recovery time is also rapid (4 minutes)

Disadvantage

- Expensive
- Not potent as a sole anesthetic; it must be used with more potent anesthetics to produce full surgical anesthesia

Uses of nitrous oxide

- To maintain surgical anesthesia (50-66%) with other agents.
- Nitrous oxide, in subanesthetic dose, provides analgesia e.g. in obstetrics, in emergency treatment of injuries and in changing painful dressings.
- N_2O must always be mixed with at least 30% oxygen to avoid hypoxia.
- For analgesia, 50% N_2O with 50% oxygen can be effective

Adverse effects

- Nausea and vomiting

- Prolonged exposure can cause megaloblastic bone marrow changes due to interference with vitamin B12 action
- Prolonged and repeated exposure of staff and patients, is associated with bone marrow suppression and a teratogenic risk.
- Nitrous oxide has a dangerous effect if used in patients with air-containing closed space e.g. pneumothorax since nitrous oxide diffuses into such spaces resulting in increased pressure that compromises respiration.

2. Halogenated anesthetics

Halothane was the first to be used

Now, superseded by isoflurane and sevoflurane

a. Halothane

- Has the highest solubility with slow induction and recovery
- Pleasant to breathe, non-irritant
- Reduces cardiac output more than others
- Sensitizes the heart to arrhythmic effect of catecholamine (arrhythmias are common)
- Moderate muscle relaxation
- 20% metabolized
- Halothane can induce hepatic enzymes and cause hepatic damage. Severe hepatoxicity can follow halothane anesthesia particularly after repeated exposure (avoid repeated exposure within at least 3 months)

b. Isoflurane

- A volatile colorless liquid
- Not flammable

- Can cause bronchial irritation (cough, breath-holding, laryngospasm)
- Minimally metabolized (0.2%)
- Causes respiratory depression
- Causes peripheral vasodilation and lowers BP
- Does not sensitize the heart to catecholamine, heart rhythm is stable.
- Relaxes voluntary muscles

c. Sevoflurane

- Only 2.5% is metabolized
- Less soluble than isoflurane in blood; rapid acting, rapid recovery
- Very pleasant to breathe, non-irritant (good choice in children)

3. Intravenous General Anesthetics

a. Propofol

- The most widely used i.v. anesthetic for induction and maintenance in adults and children
- Induction within 30 seconds, smooth and pleasant
- Recovery is rapid with less hangover effects than other i.v. anesthetics
- Causes pain on i.v. injection
- Nausea and vomiting are extremely low
- Causes a fall in blood pressure
- May cause significant extraneous muscle movements

b. Thiopental sodium (thiopentone sodium)

- Very short acting barbiturate
- Smooth induction

- Rapid distribution: initial half-life is 4 minutes, terminal t1/2 is 11 hours
- Significant accumulation in fat on repeated doses
- Nausea and vomiting slightly higher than propofol
- pH of thiopental solution is alkaline (11) and extravasation causes considerable local damage
- Accidental intra-arterial damage causes arterial spasm
- Has no analgesic activity
- Sedative effect can persist for 24 h

Methohexitone is a barbiturate similar to thiopental but shorter terminal t1/2

c. Etomidate

- Rapid recovery without hangover
- Less hypotension than thiopental and propofol during induction
- Produces high incidence of extraneous muscle movement

d. Ketamine

- Is a phencyclidine (hallucinogen) derivative
- Is an antagonist of the NMDA receptors producing a trance-like state known as dissociative anesthesia (sedation, amnesia, dissociation, analgesia)

Advantages

- Anesthesia persist for 15 minutes after a single i.v. injection, and characterized by profound analgesia.
- Has good analgesic properties in sub-anesthetic doses in contrast to most other anesthetics, ketamine usually causes:
- tachycardia, increased blood pressure and cardiac output (popular to induce anesthesia in shocked patients)

- Pharyngeal and laryngeal reflexes are only slightly impaired
- It is a potent bronchodilator

Disadvantages

- Hallucination with delirium and nightmares can occur during recovery , particularly in adults (the main disadvantage). This is reduced by giving a benzodiazepine
- No muscle relaxation; high incidence of extraneous muscle movements
- Causes increased intracranial pressure and intraocular pressure
- Has abuse potential and can cause dependence

Uses of ketamine

It is particularly valuable for children requiring frequent anesthesia.

Subanesthetic doses can be given to provide analgesia for painful procedure such as dressing of burns, radiotherapy, …

Contraindications

Moderate to severe hypertension, CHF and history of stroke

Cerebral trauma

Eye injury

Psychiatric disorders

In pregnancy before term; because it has oxytocic activity

The inhalational Anesthetic	Advantages	Disadvantages
Halothane	Pleasant to breathe, moderate muscle relaxation	Cardiac arrthymias, hepatotoxicity, slow recovery
Isoflurane	No arrhythmias No hepatotoxicity Relax voluntary muscles Lack epileptogenic property of enflurane	Bronchial irritation May precipitate myocardial ischemia in patients with coronary disease (steal phenomenon)
Sevoflurane	Rapidly acting/rapid recovery Very pleasant to breathe No arrhythmias No hepatotoxicity	Can be nephrotoxic

The i.v. anesthetic	Advantage	Disadvantage
Propofol	Pleasant induction/rapid recovery Less hangover effect Nausea and vomiting very low incidence	Fall in blood pressure Causes extraneous muscle movement
Thiopental	Rapid smooth induction	Nausea and vomiting more than propofol No analgesic effect Liable to accumulate, hangover effect for 24h Local damage, arterial spasm
Etomidate	Rapid induction and recovery No hangover Cardiovascular stable	High involuntary movements Suppresses steroid formation Pain on injection

The i.v. anesthetic	Advantages	Disadvantages
Ketamine	Potent analgesic Preferred in shocked patient	Hallucination, delusion, nightmares Tachycardia, increase BP and cardiac output (advantage in shock) No muscle relaxation High involuntary movements Increased intracranial pressure Raised intraocular pressure Slow onset (2-5 min)

22. Local anesthetics

I. **Overview**: Local anesthetics reversibly block impulse conduction along nerve axons. This can be utilized clinically to block pain sensation to a specific area of the body.

Local anesthetics can be classified according to their chemical structure into esters or amides. Each consists of a lipophilic aromatic ring connected to hydrophilic end by an ester or amide.

Examples:

a. Esters: cocaine, procaine, benzocaine and tetracaine
b. Amides: lidocaine, prilocaine and bupivacaine

The esters are metabolized by hydrolysis by the action of cholinesterase enzyme mainly in the plasma, while the amides metabolized mainly by the liver following their systemic absorption

II. **Mechanism of action of local anesthetics:**

Blocking of sodium ion channels, this will lead to increase in the threshold of excitability.

1. Prevent the initiation and conduction of nerve impulses
2. Blocks the conduction by sensory, autonomic and motor nerve endings
3. The fibers in the nerve trunks are affected in order depends on diameter size, the smallest (autonomic) fibers affected first, followed by sensory fibers and lastly the motor fibers. Clinically there is loss of pain and temperature followed by loss of touch and finally movement.

III. **Pharmacokinetics:**

Distribution depends on diffusion in the tissue and blood flow and the type of drug. Local injection acts within 5 minutes and may last up

to 1.5 hour. This duration can be doubled by the use of vasoconstrictor drugs in combination with the local anesthetic. Absorption from the site of application will terminate the action of the local anesthetic agent.

Prolongation of the action of local anesthetic:

This can be achieved by giving the local anesthetic with a vasoconstrictor drug usually adrenaline. Adrenaline will cause vasoconstriction at the site of injection and will delay the absorption of the anesthetic and prolonged its duration of action.

The combination should not be applied to the end organs such as the fingers, nose and toes, because it may cause severe vasoconstriction and cut the blood supply which will lead to gangrene of the finger. Also enough amount of adrenaline can be absorbed to the systemic circulation and lead to elevation of blood pressure and cardiac dysrhythmias. Therefore the combination should be avoided in patients with heart disease and hypertension.

Felypressin is an alternative vasoconstrictor to adrenaline. It is synthetic analogue of vasopressin causes less elevation of blood pressure and causes less tachycardia

IV. Methods of local anesthetics application:

1. Surface anesthesia as solution, cream, ointment, spray and gel, applied locally to the mucous membranes (vaginal, rectal, laryngeal) the eyes and the nose. Local anesthetics have little effect on the intact skin but can be effective in case of burns or skin lacerations
2. Infiltration anesthesia to paralyse sensory nerve endings and small cutaneous nerves, in this case the anesthetic is injected into the tissue

3. Nerve block, can anaesthetize a region as brachial plexus, paravertebral nerves or individual nerves as ulnar, sciatic or pudendal block.
4. Intravenous regional anesthesia. A cuff applied to the arm and inflated above arterial pressure and the vein filled with local anesthetic e.g.0.5-1% lidocaine. The arm in anaesthetized in 6-8 minutes and the effect last for up to 40 minutes if the cuff remained inflated.
5. Extradural block. Used in thoracic, lumbar and sacral regions. The drug is injected in the extradural space and acts on the nerve root, used mainly in obstetrics.
6. Spinal anesthesia. The drug is injected intrathecally and the patient is tilted. Hypotension occurs due to sympathetic block and headache due to CSF leakage.

V. Adverse effects of Local anesthetics:

1. excessive systemic absorption causes nervousness, tremor, anxiety and even convulsions. Respiratory depression also may occur.
2. myocardial depression, conduction block and hypotension
3. local allergic reactions as skin rash.

VI. Individual local anesthetics

1. Lidocaine (xylocaine):

Is an amide has a half-life of about 1.5 hour. It is the drug of choice for surface anesthesia as well as for injection, it combines efficacy with low toxicity. It is also useful in the treatment of cardiac dysrhythmias especially ventricular arrhythmias (classified as class IB, sodium channel blockade with shortening of the refractory period). This antiarrhythmic effect is due to blockade of sodium ion channels in the cardiac conduction system

2. **Prilocaine:**

   Use is similar to lidocaine, but it is less toxic and can be mixed with lidocaine to form an emulsion that penetrate skin and used for dermal anesthesia.

3. **Bupivacaine:**

   Is long acting and used for peripheral nerve blocks in general, including epidural and spinal block.

4. **Cocaine:**

   Is used only as surface anesthetic as 4% solution. It has many adverse effects when injected. It causes adverse effects even in surface anesthesia. Cocaine blocks the uptake of catecholamines (similar to tricyclic antidepressants) this can cause vasoconstriction. All other local anesthetics don't have this action.

   Cocaine in addition to local anesthetic effects has direct central effects as it cause euphoria and excitement and it can cause dependence.

5. **Bupivacaine**:

   has long duration of action used for nerve block including obstetric epidural anesthesia and spinal an aesthesis

6. **Procaine:**

   has short duration of action and is less used

7. **Amethocaine (tetracaine):**

   Useful in topical application and is rapidly absorbed, should be avoided in damage skin, useful in ophthalmology

8. **Mepivacaine**:

   Used in dentistry with or without adrenaline

23. Muscle Relaxants

I. Overview: Muscle relaxation can be produced:

1. By interference with neuromuscular transmission through two main mechanisms:
   a. competition with acetylcholine at the motor end plate (e.g. pancuronium, atracurium, vecuronium)
   b. depolarization of the motor endplate (e.g. suxamethonium)
2. By an action on the CNS (e.g. baclofen)
3. By direct action on the muscle itself (e.g. dantroline).

A. Competitive Antagonists

- These are competitive antagonists of acetylcholine at the motor end plate (nicotinic receptors) and result in paralysis
- Reversal can be achieved with anticholinesterase drugs such as neostigmine (too much neostigmine can itself cause NM block by depolarization)

Examples of competitive (non-depolarizing) antagonists:

1. Atracurium
   a. is altered spontaneously in the body to inactive form that is why it can be given in patients with hepatic or renal disease and in the aged patients
   b. at high doses, can cause histamine release with hypotension and bronchospasm
   c. duration of action is 15-30 minutes

2. Pancuronium

a. is the first steroid-derived neuromuscular blocker discovered
b. slightly longer acting than vecuronium
c. causes histamine release

3. **Vecuronium**

- is a steroid derivative, duration of action 30 minutes
- no cardiovascular side effects
- no histamine release

4. **Rocuronium**

- rapid onset of action (60 seconds) to allow tracheal intubation

B. Depolarizing neuromuscular blockers

Suxamethonium (succinylcholine)

- Most rapid onset (in less than 60 seconds)
- Has the shortest duration of action (4 minutes)
- Recovery occurs in about 10 minutes
- Ideal if fast onset and brief duration of muscle relaxation is needed e.g. tracheal intubation
- Suxamethonium is destroyed by plasma pseudocholinesterase. This enzyme can be genetically defective, thus paralysis may last for hours.
- Paralysis is preceded by muscular fasciculation. This can cause muscle pain (that is why it should be given after anesthetic induction).
- Suxamethonium depolarization causes release of potassium from muscles. This may be a problem in patients with high potassium levels as in acute renal failure, and in major burns sufficient to cause cardiac arrest

II. Uses of neuromuscular blocking drugs

(Used only if tracheal intubation and ventilation of lungs can be undertaken)

- To provide muscle relaxation during surgery

  Occasionally used to assist ventilation in intensive care units.

III. Reversal of neuromuscular blockade

Anticholinesterases reverse the effects of non-depolarizing (competitive) neuromuscular drugs but prolong the action of the depolarizing drugs such as suxamethonium. Edrophonium (for diagnosis) and neostigmine are used.

IV. Selective Relaxant Binding Agents (SRBAs) are a new class of drugs that selectively encapsulates and binds neuromuscular blocking agents (rocuronium>vecuronium>>pancuronium). The first drug introduced is sugammadex.

Sugammadex is a modified gamma cyclodextrin that specifically encapsulates and binds to the competitive neuromuscular blocking agents rapidly reversing their action.

V. Other muscle relaxants

- They are not useful for surgery (full relaxation is accompanied by cerebral depression).
- They can reduce spasm of the voluntary muscles without impairing voluntary movement.
- They are useful in spastic states, low back syndrome, and rheumatism with muscle spasm.

Examples

1. Baclofen

It is structurally related to GABA

It inhibits reflex activity mainly in the spinal cord

It reduces spasticity and flexor spasms

2. Dantrolene

Dantrolene acts directly on muscles and prevent the release of Calcium from muscle stores. It is given i.v. in malignant hyperthermia. Malignant hyperthermia can occur during or immediately after general anesthesia and may be precipitated by potent inhalation agents or by suxamethonium. The mechanism involves sudden release of the stored calcium of the sarcoplasm which stimulates contraction and hypermetabolic state. This release is counteracted by dantrolene

Drugs with muscle relaxing properties

Examples

1. Diazepam (and other benzodiazepines)
2. Orphenadrine (centrally-acting antimuscarinic drug)
3. Carisoprodol (is a centrally acting skeletal muscle relaxant)

24. Drugs used in gastrointestinal diseases

Drugs used in peptic ulcer

The main drugs used in the treatment of peptic ulcer include the following:

1. Antacids; magnesium salts, aluminium salts, calcium carbonate and sodium bicarbonate
2. Antihistamine (H2-antagonists) as cimetidine, ranitidine, famotidine
3. Proton Pump Inhibitors as omeprazole, lansoprazole and pentaprazole
4. Mucosal protective agents as sucralfate, bismuth chelate
5. Prostaglandins analogues as misoprostol
6. Antimuscarinics as pirenzepine

Antacids:

Acts by raising intrgastric PH and therefore reduce irritation by gastric acid secretion, they are useful in symptomatic treatment and has no effect on ulcer healing. Antacids are divided into two groups:

a. Systemic antacids; as sodium bicarbonate

b. Non-systemic as magnesium salts, aluminium salts and calcium carbonate

Sodium bicarbonate:

Has a rapid onset of action, its systemic antacids which can be absorbed systemically and alter the PH of the extra cellular fluid and may cause systemic alkalosis especially in patients with renal failure. It can also increase the absorption of calcium from the GIT lead to hypercalcemia. The excessive sodium may lead to hypernatremia and edema. When interact with gastric acid sodium bicarbonate release CO2 which cause abdominal distention.

Magnesium salts:

As magnesium trisilicate and magnesium hydroxide

Both have slow onset of action due to their insolubility. The magnesium salts can cause diarrhea due to osmotic effect. They are not absorbed systemically.

Aluminium salts:

As aluminium sulphate and aluminium hydroxide. They also not absorbed systemically but they can bind to phosphate in the GIT, so they can be used to reduce phosphate absorption in case of hyperphosphatemia of renal failure. In normal individual they may cause hypophosphatemia

Clinical uses of antacids:

1. symptomatic treatment of peptic ulcer to relief pain but they don't promote healing
2. dyspepsia due to esophageal reflex or other causes

Interactions with antacids:

1. antacids can bind to drugs in the GIT and reduce their absorption such as iron, tetracycline and digoxin
2. systemic antacids may change urine PH and increase excretion of drugs as salicylates (weak acid)

H2-receptors antagonists:

Cimetidine , Ranitidine, Famotidine

They act by blocking H2-receptors in the parietal cells in the stomach and therefore inhibit acid secretion. They reduce the volume of acid secretion and also increase the PH of the acid (make the lumen of the stomach more alkaline), they relief symptoms and promote healing in peptic ulcer

Pharmacokinetics:

Cimetidine is well absorbed when given orally, half-life about 2 hours. Partly metabolized in the liver but mainly excreted unchanged by the kidney. The half-life increase up to 5 hours in case of renal failure.

Clinical uses:

1. peptic ulcer as they promote healing of peptic ulcer and reduce relapse rate

2. reflux esophagitis

Adverse effects

1. Diarrhea and skin rash

2. Dizziness and mental confusion in the elderly

3. Gynaecomastia due to anti-androgen effect

4. Cimetidine is an enzyme inhibitor which inhibits the metabolism of other drugs as warfarin, phenytoin and theophylline.

Ranitidine: less enzyme inhibitor than cimetidine, and fewer incidences of adverse effects

Famotidine: less adverse effects than cimetidine, less enzyme inhibition and longer half-life

Proton Pump Inhibitors:

Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole

Inactivate H^+/ K^+ -ATPase (proton pump) in the parietal cells, which is the final common pathway for acid secretion by the parietal cell .They are more potent than all the other antiulcer drugs, as they inhibit the final step in acid secretion. They also promote healing of the ulcer

Omeprazole:

Is a pro-drug it enters the parietal cell from the blood by non-ionic diffusion, but become ionized inside the cells. It binds to the sulfhydryl (-SH) group in the H^+/ K^+ -ATPase pump, this irreversibly inactivates the pump causing inhibition of acid secretion.

Omeprazole is given orally, and because it's degraded by the acidic medium in the stomach it's given in enteric coated tablet. Used in peptic ulcer and Zollinger-Ellison syndrome (gastrin secreting tumor of the pancreas)

Adverse effects:

1. nausea, headache diarrhea and skin rash

2. omeprazole inhibits drug metabolizing enzymes, decreasing the metabolism of warfarin, phenytoin, carbamazepine and diazepam.

3. Chronic use of proton pup inhibitors may change the acid medium of the stomach and was shown in experimental animals to cause gastric carcinoma, also the hypochlorhydria enhances the growth of bacteria in the stomach, and these may activate carcinogens.

4. chronic hypochlorhydria also decrease the absorption of vitamin B12 which leads to megaloblastic anemia

Misoprostol:

Is a synthetic analogue of prostaglandin E1, protect against the formation of gastric and duodenal ulcer in patients taking NSAIDs. Misoprostol also can heal gastric and duodenal ulcers not related to NSAIDS.

Mechanism of action:

a. improving blood supply to the gastric mucosa

b. enhancing gastric secretion of mucous and bicarbonate

c. enhances cell replication in gastric mucosa

It is usually given in combination with NSAIDs and sometimes in fixed combination to susceptible individual to prevent gastric damage, especially with the non-selective COX- inhibitors as indomethacin and diclofenac sodium

Adverse effects:

a. Diarrhea and abdominal pain

b. vaginal bleeding and dysmenorrhoea (contraindicated in pregnancy, may lead to abortion)

Sucralfate:

Its complex salt of sucrose sulphate and aluminium hydroxide

At low PH of the stomach sucralfate form a polymer that binds to protein molecules transudate from the damaged mucosa of the ulcer area. This results in the formation of viscous paste that adheres to the ulcer base. Sucralfate can also bind to pepsin and bile salts in the stomach. It has an equal efficacy to H2-antagonists.

Adverse effects:

It's well tolerated, but may cause constipation. Aluminium blood concentration may increase and toxicity occurs specially in patients with renal failure.

The drug is effective only in acid medium and therefore should not be given in combination with antacids. Sucralfate can reduce the intestinal absorption of ciprofloxacin, theophylline, digoxin and phenytoin.

Bismuth Chelate:

Tripotassium-dicitrobismuthate, bismuth sub-citrate (De-Nol)

Acts by chelating with protein in the ulcer base to form a coating in the ulcer base, which protects the ulcer from acid, pepsin and bile. In addition it has a valuable action against *Helicobacter pylori* . Has similar efficacy to cimetidine but in addition it causes less chances of recurrence due to bacterial eradication.

Adverse effects:

Liquid dosage form causes dark discoloration of the tongue and mouth, occurs less with tablets. There is little systemic absorption, but bismuth may accumulate in patients with renal failure.

Anticholinergic drugs:

Pirenzepine, probantheline,

These agents reduce the volume of gastric acid secretion without affecting the PH. They produce symptomatic relief in peptic ulceration, but they do not enhance ulcer healing.

Pirenzepine is water soluble and does not penetrate the CNS and has no central side effects. It also selective to muscarinic (M1) receptors in the gastric mucosa

All the anticholinergics have atropine like adverse effects.

Helicobacter pylori eradication in peptic ulcer:

Colonization of the stomach and duodenum occurs in almost all patients with duodenal ulcer and in the majority of patients with gastric ulcer. The chronic infection with *H.Pylori*, which establishes itself within the mucous layers, is associated with increase secretion of acid and gastrin. Not every patient with infection will develop ulcer as there are other host factors which might be important.

Successful eradication of helicobacter pylori usually results in long-term remission of the ulcer as re-infection rates are low. The organism is sensitive to the following:

Metronidazole, **amoxicillin**, **clarithromycin**, **tetracycline** and **bismuth salts**

These drugs are used in various combinations in order to ensure eradication and reduce the chance of resistance, and usually they are given in combination with an antiulcer drug as omeprazole, ranitidine or bismuth citrate.

Examples:

Omeprazole 20 mg b.d + Clarithromycin 500mg b.d. + Amoxicillin 1g B.d. For 7 days, or Omeprazole 20 mg bd + Clarithromycin 500 mg b.d. + Metronidazole 400 mg b.d. For 7 days

NSAIDs and Peptic ulcer:

Large number of patients taking NSAIDS such as aspirin, diclofenac sodium, and indemetacin. Gastric erosion developed in about 80% of these patients and about 1-5% developed gastric or duodenal ulcer. These drugs inhibits cyclooxygenase enzyme in its both types (COX1 and COX2). COX1 is important for the development of gastric mucosa, while COX2 mediates inflammatory reactions.

Inhibition of COX1 will lead to gastric and duodenal mucosal injury and cause peptic ulceration. The prostaglandin analogue misoprostol is useful in the prevention and treatment of such ulcer, it also be treated with other anti-ulcer drugs.

The use of selective COX2 inhibitors as rofecoxib and celecoxib is less likely to cause mucosal damage and are preferred in patients with peptic ulcer.

Laxatives and Purgatives:

Laxatives, purgatives and cathartics are similar, they are the drugs used to promote or help defaecation by reducing the viscosity of the contents of the lower colon or stimulate colonic contraction and are classified as:

1. Bulk laxatives
2. Osmotic laxatives
3. Faecal softeners
4. Stimulant laxatives

1. Bulk Laxatives:

Bran and **methyl cellulose**

Acts by increasing the volume and reducing the viscosity of the intestinal contents which lead to effective reflex bowel activity.

Bran is the residue left when the flour is made from cereals. It contains fibers which are not digestible so enter into the colon intact. It has great capacity

for holding water increasing the volume and reducing the viscosity of the colonic contents.

2.Osmotic laxatives:

Magnesium salts, **Lactulose**, **Polyethylene glycol**

These are little absorbed and increase the bulk and reduce the viscosity of intestinal contents due to holding water by osmotic effect

Magnesium salts:

As **Magnesium sulphate** and **Magnesium hydroxide**

Acts by retaining water in the intestinal lumen and can also withdraw water from the body to the intestine. Both salts act in 2-4 hours. Magnesium sulphate is more powerful than magnesium hydroxide. Magnesium sulphate can also be given by retention enema

Lactulose:

Is a synthetic disaccharide it can be taken orally as it's not metabolized and acts as osmotic laxative. It is also used in hepatic encephalopathy as it is split into lactic and acetic acids which inhibit the growth of ammonia producing organisms and also by lowering intestinal PH can reduce diffusion of ammonia into the colon.

Osmotic laxatives can be used to clear the colon in diagnostic procedures as colonoscopy or radiology or in preparation for colonic surgery. They can be given orally or as retention enema.

3. **Faecal softeners:**

Docusate sodium and **Liquid paraffin**

Lead to softening of the faecal material which is useful in condition like haemorrhoids and anal fissure.

Docusate sodium (dioctyl sodium sulphosuccinate)

Causes softening of the faces by lowering the surface tension of fluids in the bowel, this allows more water to remain in the faces, and it also has a weak bowel stimulant effect. It takes 1-2 days to act.

Liquid paraffin:

Is an inert mineral oil which is not digested, it promotes the passage of soft faecal matters. May be aspirated and cause lipoid pneumonia.

4. **Stimulant laxatives**:

Bisacodyl, **Glycerol, sodium picosulphate** , **Senna** and **castor oil**

These drugs increase the intestinal motility by various mechanisms, they may cause abdominal cramps

Bisacodyl:

Stimulates the sensory nerve endings of the colon by a direct action from the intestinal lumen. It is effective when given orally and acts in 6-10 hours. Can also be given by suppositories especially in the elderly people, it acts in about 1 hour. Have no important adverse effects. Bisacodyl suppositories is used to obtain bowel action in 1hour

Glycerol has a mild stimulant effect on the rectum when given as suppositories

Senna:

Hydrolyzed by the liver into senoside A and B. It enhances the response of the colon to normal stimuli. It is absorbed in the small intestine and secreted in the colon so take about 8 hours to act.

Enemas:

Administered rectally, produce defecation by softening the faecal materials and distending the bowel. They are used in the preparation of patients for surgery, endoscopy and radiological examination. Preparation contains sodium sulphate are usually used.

The clinical uses of laxatives and purgatives in general include:

1. treatment of constipation
2. painful anal conditions as hemorrhoids and anal fissure, to soften the stool
3. preparation of the colon for surgery, colonoscopy and radiological examination
4. in the post-operative management of colostomy
5. irritable bowel syndrome
6. diverticular disease

Caution: Chronic use of laxatives by the elderly should be avoided in children all laxatives and purgatives should be avoided and oral rehydration fluid is more important

Antidiarrheal drugs:

1. Antimotility drugs as: **codeine, diphenoxylate** and **loperamide**
2. Drugs increase viscosity of faces as: **Kaolin**

Codeine:

Acts on the opioid receptors in the smooth muscles of the bowel to reduce peristalsis and increase segmentation contraction

Diphenoxylate:

Has an effect similar to codeine. Usually given mixed with atropine (Lomotil). It causes nausea, vomiting abdominal; pain and CNS depression.

Loperamide:

Also an opiate act by inhibiting contraction of the smooth muscles of the intestine.

It also causes nausea, abdominal pain and vomiting.

All the anti-motility drugs should not be given to children with acute diarrhea as they may cause paralytic ileus and respiratory depression.

Antiemetic drugs:

Are group of drugs used in vomiting due to different causes.

Classification:

1. Antimuscarinic drugs as **hyoscine**

2. Antihistamines as **cyclizine**, **dimenhydrinate** and **promethazine**

3. Dopamine receptors antagonists: **metoclopramide**, **domperidone**, **Phenothiazines as prochlorperazine and haloperidol**

4. $5HT_3$ receptors antagonists: **ondansetron, granisetron**

5. Other agents: **cannabinoids**, **corticosteroids**

6. Neurokinin receptor (NK1) antagonist as **aprepitant**

Metoclopramide:

Acts centrally by blocking dopamine D_2 receptors in the chemo-receptors trigger zone, and peripherally by enhancing acetylcholine action at muscarinic nerve ending in the gastrointestinal tract. It increases the tone of the lower esophageal sphincter and relaxes the pyloric sphincter and increase peristaltic movements of the intestine

Metoclopramide is metabolized by the liver with a half-life of 4 hours.

Uses:

a. nauseas and vomiting associated with gastrointestinal diseases

b. cytotoxic and radiotherapy induced vomiting

c. in migraine to relief nausea & vomiting and increase absorption of analgesics

d. to empty the stomach in emergency anesthesia

Adverse effects:

1. extra-pyramidal dystonia (torticollis, facial spasm, oculogyric crisis), more common in children and young adults (treated with benztropine i.v)

2. Diarrhea

3. stimulation of prolactin release with gynaecomastia and galactorrhea

Domperidone:

Is a selective dopamine D_2 receptors antagonist, it has no acetylcholine like action. The half-life is about 7 hours. It is used for the treatment of nausea and vomiting associated with gastrointestinal disorders and cytotoxic induced vomiting.

It may cause gynaecomastia and galactorrhoea .

Ondansetron:

Is a selective 5-HT_3 receptors antagonist. Ondansetron is highly effective against nausea and vomiting induced by cytotoxic drugs and radiotherapy (treatment of cancer with cytotoxic drugs or radiotherapy may release serotonin).

Cause constipation, headache and facial flushing.

Corticosteroids as dexamethasone are also effective in cytotoxic drugs induced vomiting, probably act by reducing oedema in vomiting centers or other CNS effect

Nabilone:

Is a synthetic cannabinoid. Used mainly to relief nausea and vomiting associated with cytotoxic drugs.

Adverse effects in clued dryness of the mouth decrease appetite, dizziness, postural hypotension, euphoria and dysphorea confusion and psychosis.

Hyoscine:

Is structurally related to atropine. It has a CNS depressant effect. Its antiemetic effect is due to the antimuscarinic action and also due to its central action; it is especially effective in motion sickness (nausea and vomiting associated with travel by train, motor car or by sea). It mainly causes antimuscarinic adverse effects.

Cyclizine and promethazine are both antihistamines (H_1 receptor blockers), effective mainly in motion sickness and middle ear disorders.

Aprepitant: is anew antiemetic drug as antagonist to neurokinin receptors type1 (NK1) in the chemoreceptor trigger zone, can be given orally with a half-life of 12 hours and metabolized by the liver. Usually given in combination with other antiemetic drugs, may cause fatigue, dizziness and diarrhea.

Emetic drugs:

Are the drugs that can cause vomiting, they are especially useful in the treatment of poisoning most important is ipecacuanha

Ipecacuanha: is present as liquid it contain emetine which induce vomiting by gastric stimulation (irritation) especially useful in children

Large number of drugs cause nausea and vomiting as a side effects as opiates, cytotoxic drugs and digoxin

Ulcerative colitis:

A chronic inflammatory condition of the colon characterized by repeated attacks of diarrhea and rectal bleeding:

Drugs useful in ulcerative colitis include:

1. sulfasalazine
2. immunosuppressant
3. corticosteroids

Sulfasalazine:

Contain two compounds sulfapyridine and 5-aminosalicylic acid

It is poorly absorbed from the gut . Split by the bacteria in the colon, the active part is 5-aminisalicylic acid. The sulfapyridine cab be absorbed and acetylated by the liver, it only help delivering the drug to the site of action.

Sulfasalazine also useful as a disease modifying drug in rheumatoid arthritis

Adverse effects: are related to the sulfapyridine and include headache, malaise, nausea and vomiting and skin rash.

Mesalazine: contains only 5-aminosalicylic acid used in patients who cannot tolerate sulfonamides.

Drugs for dissolution of gall stones:

Ursodeoxycholic acid and **chenodeoxycholic acids**

Bile contains cholesterol and bile salts (bile salts increase solubility of cholesterol). Increase in cholesterol or decrease in bile salts results in the formation of cholesterol stones

1.best treatment for symptomatic gall stones is surgical removal

2. these drugs are useful in cholesterol stones only (80% of gall stones)

3. they are used in symptomatic patients

4, they act by decreasing the content of cholesterol in bile, by inhibiting the enzyme involved in cholesterol formation

25. Drugs Acting on The Respiratory System

Drugs can be used:

to treat cough

to dissolve sputum (Mucolytics)

as respiratory stimulants

as respiratory surfactants

to treat bronchial asthma

Others

Cough is of two types:

Useful (to expel secretions or foreign bodies from respiratory tract: productive cough)

Useless (unproductive and persistent)

Useful (productive) cough should **NOT** be stopped unless it is exhausting to the patient or dangerous e.g. after eye surgery

Cough suppression

1. **Antitussives that act peripherally**

Simple linctuses and lozenges making a soothing coat on the pharynx (demulcents), used for above the pharynx causes.

- **Steam inhalation,** acts by promoting a dilute mucus secretion and by protecting inflamed mucosa. An aromatic compound e.g. benzoin tincture, menthol or eucalyptus, may be added (menthol can block an ion channel TRPV1); TRPV1= Transient receptor potential vanilloid 1.
- **Topical local anesthetics** in the airways to block the mucosal cough receptors.

2. **Antitussives that act centrally**

They act by blocking the medullary cough center. Sedation may also contribute to their action:

- Opioids (codeine and methadone)

- Dextromethorphan and pholcodeine: have antitussive effect which is not blocked by naloxone (non-μ-type opiate receptors may be involved). They can be used orally and as linctuses.

Sedation can reduce the sensitivity of cough reflex (sedating antihistamines e.g. diphenhydramine and promethazine, can suppress cough by non-H1 receptor action).

The underlying conditions should be treated, for example, a common cause of dry cough in patients with hypertension and heart failure, is ACEIs (This cough can be stopped by stop taking the ACEIs such as captopril or switch to angiotensin-receptor blockers e.g. losartan)

Mucolytics

In conditions such as cystic fibrosis and bronchiectasis, there is difficulty in clearing the chest of viscous sputum because the bronchial cilia are ineffective. Drugs that liquefy mucus (mucolytics) can provide benefit.

1. Carbocysteine: It has free SH groups that open disulphide bonds in mucus and reduce its viscosity. It is given orally or by inhalation and may cause GI irritation and allergic reactions

2. (Bisolvon, Solvodin)

It increases the proportion of serous bronchial secretion making it easily expectorated.

3. Water inhalation via an aerosol (breathing over a hot basin), is an effective expectorant therapy.

Hydrating a dehydrated patient can also lower sputum viscosity.

Expectorants

These encourage productive cough by increasing the volume of bronchial secretion. Examples: guaifenesin (glyceryl guaiacolate), and volatile oils. They are of questionable clinical benefit

Cough mixtures may contain several compounds such as antitussives, expectorants, mucolytics, bronchodilators, sedatives, decongestants or glycerol.

Respiratory stimulants (Analeptics)

They are CNS stimulants, that can cause convulsion in doses just above their therapeutic doses (need careful monitoring)

- **Doxapram** (given by infusion)
- **Aminophylline** (a complex of theophylline and EDTA), acts also as respiratory stimulant and given slowly i.v.

Respiratory stimulants can be used in:

Respiratory failure with hypercapnea, drowsiness and inability to cough.

Apnea in premature infants (aminophylline and caffeine may benefit some cases)

Respiratory stimulants should be avoided in:

Epilepsy

Ischemic heart disease

Acute severe asthma

Severe hypertension

Thyrotoxicosis

The use of non-invasive nasal positive- pressure ventilation for respiratory failure has reduced the role of respiratory stimulants in its management.

Pulmonary surfactants

The endogenous surfactant system produces low surface tension in the alveoli preventing their collapse. Deficiency of this natural surfactant

occurs in Respiratory Distress Syndrome. Synthetic phospholipids are now used for intra-tracheal instillation as a surfactant.

Example: Colfosceril palmitate (should be stored chilled)

Bronchial Asthma

Bronchial asthma is a chronic inflammatory condition resulting in hyperactive bronchi in response to different stimuli (e.g. allergens, viruses, environmental chemicals such as ozone, …). Inflammatory mediators are liberated from mast cells and from other cells (histamine, prostaglandins, leukotrienes, platelet-activating factor, …)

Treatment of Bronchial Asthma

Objectives of treatment

Prevention of exposure to allergen(s)

Reduction of the bronchial inflammation and hyperactivity (Glucocorticoids, cromoglicate, ketotifen)

Dilatation of the narrowed bronchi (β2-agonists, theophylline, ipratropium)

Prevention of bronchoconstriction (montelukast)

(A) Reduction of the bronchial inflammation and hyperactivity

Glucocorticoids

- are the cornerstone of asthma treatment
- cause a gradual reduction in inflammation and hyperactivity

Mechanism: : inhibit the release of mediators from macrophages and eosinophils and the induced leakage from the microvasculature. They also inhibit influx of inflammatory cells into the lungs

Types of glucocorticoids used in asthma:

Inhalation: e.g. beclomethasone, fluticasone, budesonide (long duration)

Oral e.g. prednisolone (intermediate duration)

Intravenous: e.g. hydrocortisone (i.v. short-acting)

Inhaled glucocorticoids: ex. beclomethasone, fluticasone and budesonide

- They are used for long term prophylaxis of chronic asthma. They are less effective in acute attacks.
- They have marked local action on bronchi with low systemic effects due to poor absorption and due to extensive first pass metabolism when swallowed. Their systemic side effects are, therefore, minimal. Lower doses are required because of their high potency and their direct local effect which further reduce their systemic side effects .

  Side effects : hoarseness, dysphonia and oropharyngeal candidiasis. These can be minimized by rinsing the mouth with water after each use.

2. Sodium cromoglicate

Actions

Inhibits the late allergic response and hyperactivity (pointing to an effect on inflammatory cells other than mast cells, and also on local axon reflexes important in asthma). It also inhibits the release of mediators from mast cells. It is poorly absorbed from the GIT, but well absorbed from the lungs. It is given by inhalation as powder, aerosol, or nebulizer. Eliminated unchanged in urine and bile. It is not effective in terminating an acute attack because it is used to prevent bronchoconstriction rather than inducing bronchodilatation). It has low toxicity. It may cause cough and bronchospasm after inhalation. It can also be used in the eye and nose.

Nedocromil has similar actions to cromoglicate but is structurally unrelated to it.

3. Other drugs:

Ketotifen: is an H1-blocker and may have anti-asthma effect (stabilize mast cells)

(B) Dilatation of narrowed bronchi

β2-Adrenoceptor agonists. Stimulation of β2-receptors results in stimulation of adenylate cyclase, increasing cAMP level resulting in smooth muscle relaxation and bronchodilatation. It also stabilizes mast cells.

Short-acting β2 – stimulants: Salbutamol, terbutaline

Long-acting β2 – stimulants: Salmeterol, rimiterol, formoterol

Salbutamol has a short duration of 4 hours and can be administered orally, i.v. or by inhalation.

Salmeterol has a long duration of 12 hours and is only administered by inhalation. It is not effective in acute attack because it has a slow onset of action (20 minutes). Salmeterol is used for prophylaxis of bronchial asthma. Since corticosteroids increase sensitivity of beta-2 receptors to beta 2 agonists, they may be given together. Tolerance for salmeterol does not usually occur.

Side effects of β2-agonists

Tremor (fine, particularly in the hands), nervous tension, hypokalemia and hyperglycemia due to stimulation of β-2 receptors.

Tachycardia, palpitation, and arrhythmia (β1)

They are used when needed because continuous use, down-regulates bronchial β2-receptors resulting in tolerance. Overuse of β2-adrenergic agonists may be associated with increased risk of death in asthma

Less selective adrenoceptor agonists such as isoprenaline, orciprenaline, adrenaline, ephedrine, .. are less safe and are more likely to cause cardiac arrhythmias

2. Theophylline, a methylxanthine derivative

Pharmacological effects

Bronchodilatation

Positive inotropic and chronotropic effects

Mild diuretic effect

CNS stimulant effect

Mechanism of action

-Inhibition of phosphodiesterase especially its type 4 isoform.

-Antiinflammatory effect

-Blockade of adenosine receptors

Theophylline kinetics

Rapid and complete absorption

90% metabolized in the liver, saturable at therapeutic doses

Half-life is about 8 h, prolonged in cardiopulmonary diseases and cirrhosis, obesity and prematurity. Smoking can increase its elimination by enzyme induction

Theophylline requires TDM because of low therapeutic index and pharmacokinetic variation.

It is relatively insoluble. Solubility is increased by either being formulated as a salt with choline (choline theophyllinate) or complexed with EDTA (aminophylline). Aminophylline is soluble and can be given in acute severe asthma. It is administered I.V. slowly – a loading dose of 5mg/kg over 20 minutes.

Always enquire about taking any of the methylxanthine preparations by the patient before injecting aminophylline. If the patient is already taking these drugs, the loading dose should be avoided.

Adverse effects

Nausea and vomiting

Gastric irritation and diarrhea

Cardiac arrhythmias

Convulsion

Overdose: vomiting, arrhythmias, hypokalemia, convulsion

3. Antimuscarinic bronchodilators

Vagally-mediated bronchoconstriction is due to release of Ach at M3 muscarinic receptors. Blocking these receptors by antimuscarinic drugs results in bronchodilatation. The preferred antimuscarinic drugs are: ipratropium, oxitropium and the long-acting tiotropium (24 h).

These drugs are permanently charged with no significant absorption after inhalation (local effect). Thus, systemic antimuscarinic effects and side effects are minimum. Used mostly in older patients with chronic obstructive pulmonary disease and in acute rather than chronic asthma

4. Leukotriene receptor antagonists

(e.g. montelukast and zafirlukast). Leukotrienes (cysteinyl-LTs, C4, D4, E4) cause bronchocostriction. Blocking LT receptors can prevent this bronchoconstriction.

Inhaled drugs have the following properties:

Much less systemic side effects, particularly corticosteroids

Much less dose is required e.g. 100 µg of salbutamol by inhalation is equivalent to 2000 µg by oral route

For a drug to be inhaled properly:

The drug must first be converted to particulate form. It is necessary to coordinate activation of the inhaler with inspiration and a final hold of breath. If unable to do that e.g. children and elderly, a spacer is used

The vehicle in which the drug is dissolved is changed from CFC (chlorofluorocarbon) which depletes atmospheric ozone into HFAs (hydrofluoroalkanes) which is ozone friendly.

Types of inhalers

- Pressurized aerosol
- Nebulizers
- Dry powder inhalers

Beta blockers can precipitate asthma and it is contraindicated in patients with asthma. Overuse of β2-adrenergic agonists are associated with increased risk of death in asthma.

26. Diuretics

Diuretics drugs increase urine (diuresis) and sodium excretion (natriuresis).

A. Classification:

1. High-efficacy (Potassium-depleting) (loop) diuretics example: furosemide, bumetanide, torasemide.
2. Moderate- efficacy (Potassium-depleting) diuretics

a. thiazides eg. Hydrochlorothiazide, bendroflumethiazide

b. thiazides- related diuretics eg. metolazone, chlorthalidone, Indapamide

3. Low efficacy diuretics

a. potassium- sparing diuretic:

1. aldosterone antagonist ex. Spironolactone, eplerenone.
2. Inhibitors of renal sodium channel ex. triamterene, amiloride.

b. osmotic diuretics ex. Manitol

c. carbonic anhydrase inhibitors ex. Acetazolamide, dorzolamide

B. Classes of drugs

1. Thiazides and thiazide- related diuretics:

Mechanism of action and site of action: Inhibit sodium reabsorption by inhibiting the Na^+/Cl^- transpoter in cortical diluting segment (the early portion of distal convoluted tubule); between ascending loop of Henle and late distal tubule.

Efficacy is moderate; they cause 5- 10% of filtered sodium to be excreted, because nearly 90% of filtered sodium has already been reabsorbed before it reaches their site of action.

Hypokalaemia occurs because more amount of sodium is delivered to the distal nephrones, where it exchanges with potassium.

'Ceiling' of effect is low -the dose response curve is flat; increasing the dose beyond a small range produces no additional diuresis.

Onset of action: slow - 2h (orally); so they are not suitable for clinical situations that require rapid diuresis i.e. acute pulmonary oedema or sever hypertension.

Duration of action: long e.g. (hydrochlorothiazide and bendroflumethiazide-12h, chlorthalidone-48 h) .The long duration of action allows once daily administration and they are preferably given early in the morning so that diuresis does not disturb patients' sleep).

They are ineffective in sever renal impairment and when GFR has fallen below 20 ml/min (except metolazone).

Chronic use reduce blood pressure in hypertensives due to thiazides-induced diuresis in addition to vasodilatation which reduces the peripheral resistance, through increasing vasodilating PGS and because reduction of Na^{+} leads to reduction in intracellular Ca^{+2} which relaxes vascular smooth muscle.

Renal calcium excretion is decreased. They are preferred on loop diuretics in calcium-deficient, elderly and osteoporotic individuals who are at risk of fractures. The hypocalcuric effect of thiazides has also been used for prevention of hypercalciuria and renal calcium stones.

Renal Mg^{+2}excretion is increased.

Serum uric acid level is increased because diuretics are organic acids and compete with uric acid for proximal tubular secretion.

USES:

1. hypertension
2. oedema due to heart failure, renal and hepatic diseases.
3. diabetes insipidus.

4. hypercalciuria with recurrent renal calcium stones

2. Loop diuretics

Furosemide is prototype

Mechanism and Site of action: inhibit sodium reabsorption by inhibiting $Na^+/K^+/2Cl^-$ transporter in the medullary thick ascending loop of Henle.

Efficacy is high; cause up to 25% of filtered Na^+ to be excreted.

'Ceiling' of effect is high (diuresis goes on increasing with increasing dose) .Over-treatment can cause dehydration.

Onset of action rapid -furosemide (i.v. 30 min), (oral 1 h); therefore it is suitable for emergency situations as acute pulmonary oedema and hypertensive crisis.

Duration of action: Short- (6h), so if given late during a day it does not disturb sleep.

Hypokalaemia occur by same mechanism as thiazides.

Loop diuretics remain effective in severe renal impairment and at GFR below 10ml/min.

Renal Ca^{+2} excretions are increased. This is utilized in treatment of hypercalcaemia. On other hand they are not preferred in elderly, osteoporotic and calcium deficient, for loop diuretics use is associated with an increased risk of fractures.

Renal Mg^+ excretion is increased.

Serum uric acid is increased (by same mechanism as thiazides).

USES:

1. acute pulmonary oedema and acute left ventricular failure
2. oedema due to renal or hepatic diseases
3. hypertensive emergencies, hypertension associated with renal failure or congestive heart failure

4. hypercalcaemia.
5. cerebral oedema.
6. renal failure

Side effects of diuretics:

a. Metabolic:

1. Hypokalaemia: risk is more with low dietary K^+ intake, concurrent use of other drugs that cause hypokalaemia as β2-adrenoceptor agonists, theophylline and corticosteroids, g.i.t. diseases that cause electrolyte loss as vomiting or diarrhea.

   Hypokalaemia causes arrhythmias.

   It can be prevented or treated by high dietary potassium intake, supplement of KCl tablets or combining potassium- depleting with potassium- sparing diuretics
2. hyponatraemia and hypovolaemia
3. hypotension
4. hypomagnaesemia
5. hypercalcaemia due to thiazides and hypocalcaemia due to loop diuretics
6. hyperuricaemia; gout may occur
7. Hyperglycemia
8. hyperlipidaemia

b. Other side effects: Thiazides: thrombocytopenia, agranulocytosis, photosensitivity, dermatitis.

   Furosemide and loop diuretics: hearing loss

   Drug interactions of loop and thiazides diuretics:

1. hypokalaemia induced by these drugs enhances digoxin toxicity.
2. NSAIDs reduce effect of diuretics by inhibiting synthesis of renal vasodilator PGs.

3. Diuretics precipitate lithium toxicity by inhibiting its excretion.
4. Loop diuretics potentiate aminoglycosides-induced ototoxicity.

3. Potassium-sparing diuretics:

Efficacy: is low; cause 5% of filtered sodium to be excreted, so they are usually given with other more efficacious diuretics.

1. Spironolactone:

Mechanism of action: is a steroid, structurally similar to aldosterone and acts as a competitive antagonist on aldosterone receptors in the late distal tubule cells, increasing Na^+ and decreasing K^+ excretion.

It is a mild diuretic because majority of Na^+ has already been reabsorbed proximal to its site of action.

Pharmacokinetics:

Metabolized in liver to active metabolite (canrenone), which prolongs the diuretic effect to 48h.

Onset of action is slow (about 4 days).

Uses:

1. Hypertension with other diuretics
2. oedema and ascites due to congestive heart failure, liver cirrhosis and nephrotic syndrome
3. primary hyperaldosteronism
4. Secondary hyperaldosteronism due to hepatic cirrhosis.
5. To counteract potassium loss due to thiazides and loop diuretics.
6. hirsutism in female due to its antiandrogen effect

Side effects:

1. Hyperkalemia
2. hormonal imbalance, Gynaecomastia, impotence, menstrual disturbance
3. Gastric upset; increased risk of gastric ulcer

Drug interactions potentiate hyperkalaemia if given with angiotensin receptor blockers or angiotensin converting enzyme inhibitors.

2. Eplerenone: aldosterone antagonist has similar action but more selective and less hormonal imbalance side effects than aldosterone.

3. Amiloride and triamterene

Inhibit Na^+ reabsorption by blocking renal epithelial Na^+ channels in late distal tubule and collecting duct.

Uses: with loop or thiazide diuretics to counteract hypokalaemia .

Side effects:

1. hyperkalaemia
2. GIT upset

4. Osmotic diuretics ex. Mannitol

Is a low molecular weight substance that is filtered by the glomerulus but not reabsorbed by the renal tubule, and thus increase the osmolarity of the tubular fluid. Thus they prevent passive reabsorption of water in the proximal tubule and loop of Henle which cause an increase in urine volume.

It is not absorbed orally and given IV.

Because they increase water rather than sodium excretion , osmotic diuretics are not useful for treating oedema and other conditions caused due to sodium retention.

USES: 1- for rapid reduction of intracranial pressure

2- to maintain urine flow in acute renal failure

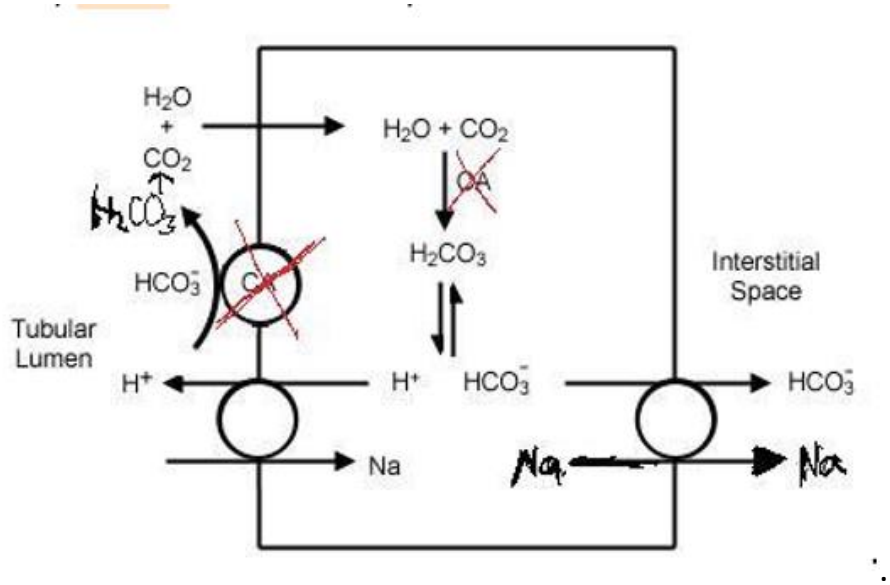
Side effects: dehydration, expansion of volume extracellular fluid

Contraindications: congestive heart failure, pulmonary oedema because it increases extra cellular fluid volume by encouraging water movement from inside cells to the extracellular fluid.

5. **Carbonic anhydrase inhibitors (CAI)** ex. acetazolamide

   Mechanism of action: inhibit Carbonic anhydrase enzyme in cells of renal proximal tubule). Thus inhibiting the formation of hydrogen and bicarbonate ions from CO2 and water, so reduces the availability of H ions for exchange with sodium and increasing excretion of bicarbonate, sodium and water. This results in alkaline diuresis.

   Diuretic effect is lost following several days, because of depletion of the body $HCO3^-$ therefore they are not used as diuretics.



USES: orally

1. treatment of chronic glaucoma (inhibition of carbonic anhydrase in ciliary body reduces formation of aqueous humor)
2. tonic-clonic, absence and partial epilepsy
3. prevention of mountain sickness
4. familial periodic paralysis

Side effects:

1. parasthesia and numbness in toes and fingers.
2. drowsiness
3. metabolic acidosis
4. Ca^{+2} renal stones, because Ca^{+2} is insoluble in alkaline urine

Dorzolamide: topical (eye drops) CAI, used in chronic glaucoma has less systemic side effects.

27. Antihypertensive Drugs

Blood pressure is determined by cardiac output and total peripheral resistance. In order to reduce blood pressure, drugs can either reduce blood volume, dilate the arterial and or the venous blood vessels, or has central effect (influence the vasomotor centers). The main groups of drugs used in the treatment of hypertension include;

1. Beta-adrenoceptor blockers: propranolol, metoprolol, atenolol
2. Diuretics: mainly thiazides
3. Angiotensin converting enzyme inhibitors as captopril, lisinopril, enalapril
4. Angiotensin receptor antagonists as valsartan, losartan
5. Calcium channel blockers; nifedipine, amlodipine
6. Alpha-adrenoceptor blockers; prazosin, doxazosin
7. Centrally acting drugs; clonidine, methyldopa,
8. Vasodilators; hydralazine, diazoxide, minoxidil, sodium nitroprusside
9. Others as reserpine, guanethidine

Drug groups

1. Beta-adrenoceptor blockers

- Non selective, propranolol
- β1-selective as **atenolol, metoprolol and acebutolol**
- α and β blockers as **labetalol, carvedilol**
- With intrinsic sympathomimetic activity (ISA) as **pindolol**

Mechanisms of Beta blockers in lowering blood pressure:

- decreasing heart rate & cardiac output
- reduce rennin release
- resetting of (baroreceptors) peripheral resistance

- CNS effect

Beta-blockers are also used in angina pectoris, cardiac dysrhythmias, thyrotoxicosis , anxiety neurosis, migraine tremor and glaucoma

Adverse effects

- CVS: bradycardia, heart block, heart failure
- Fatigue and cold extremities (reduce peripheral blood flow)
- Bronchospasm, should be avoided in bronchial asthma
- CNS: sleep disturbances, insomnia, depression, hallucination
- Diabetes; interfere with control and potentiates hypoglycemia
- Others; GI disturbances

Labetalol

- Has both β and α blocking activity (β/α 3:1)
- It is non-selective beta blockers with intrinsic activity
- Is selective α1 blocker like prazosin
- Produce reduction in the peripheral resistance with little effect on cardiac output
- Useful in chronic treatment of hypertension
- It is useful in hypertensive emergencies given i.v
- Is useful in the treatment of phaeochromocytoma (α and β blockade)
- Adverse effects include postural hypotension, GI disturbances, impotence, skin rash, bronchospasm and heart failure

2. Thiazides diuretics

- Chlorthiazide, hydrochlorthiazide, chlorthalidone
- Decrease in blood volume and cardiac output, which lead to reduction of blood pressure

- Chronic use lead to decrease peripheral resistance due to reduction of Na^+ which lead to decrease of intracellular Ca^{2+} which relax vascular smooth muscles
- Can be used alone or in combination with other antihypertensive drugs

Adverse effects include

- May cause hypokalemia, impaired glucose tolerance, hyperuricaemia and increase serum lipids
- Potassium sparing as amiloride can be combines with thiazides to avoid hypokalemia

Loop diuretics

Furosemide, bumetanide

- Are used in sever hypertension
- In case of renal impairment
- When hypertension is associated with heart failure
- In emergency lowering of blood pressure

3. Angiotensin converting enzyme inhibitors (ACEIs)

Captopril, enalapril, lisinopril

- Inhibits angiotensin converting enzyme
- Reduce conversion of angiotensin I to angiotensin II produce arterial dilatation & reduce total peripheral resistance
- Dilates the veins and reduce venous return to the heart and hence reduce cardiac output
- Reduce aldosterone secretion and decrease fluid retention (also reduce cardiac output)
- They are useful in hypertension and heart failure

- Adverse effects include first dose hypotension, hyperkalemia (due to reduce aldosterone) , dry cough (increase bradykinin), agranulocytosis, skin rash, reduction or loss of taste and angioedema, proteinuria
- ACEIs are contraindicated during pregnancy as they can cause congenital anomalies

4. A. Angiotensin receptor antagonists; losartan, valsartan

Acts by blocking angiotensin II receptors (AT1)

- have similar pharmacological effects to ACEIs
- Lower blood pressure by reducing preload and afterload
- Are used when patients cannot tolerate side effects to ACEIs specially cough

B.Direct rennin inhibitors; aliskiren

This drug inhibits the rennin-angiotensin system at its origin. Aliskiren is a potent competitive inhibitor of renin, so it blocks the conversion of angiotensinogen to angiotensin I and therefore reduces the production of angiotensin II . It also decrease aldosterone secretion

5. Calcium channel blockers

- Nifedipine, amlodipine
- Nifedipine and amlodipine act more on the vascular smooth muscles, with little effect on the cardiac muscles
- diltiazem and verapamil acts more on cardiac and vascular smooth muscles
- Inhibit intracellular calcium ion influx
- Lead to vasodilatation and decrease peripheral resistance
- Mainly arteriolar dilators, but also dilate veins
- Have negative inotropic effect on the heart

- Useful in angina, myocardial infarction (cause coronary vasodilatation) and dysrhythmias
- Adverse effects: dizziness, hypotension, flushing and ankle edema, disturbances of cardiac conduction

6. Alpha-adrenoceptor blockers

- Prazosin, doxazosin
- Selective α1-adrenoceptors blockers lead to vasodilatation with less tachycardia and reduction of blood pressure
- Are also useful in benign prostatic hypertrophy (relaxation of the bladder sphincter)
- Adverse effects ; postural hypotension, headache, dry mouth, dizziness, impotence and skin rash
- Non-selective α-blockers as phentolamine and phenoxybenzamine cause reflex tachycardia and used mainly in phaeochromocytoma

7. Centrally acting antihypertensive:

A. Methyldopa is centrally acting α2-receptor agonist (converted into α-methylnorepinephrine which acts as agonists at α2 adrenoceptors) , reduce NA secretion and sympathetic out flow in the vasomotor centers in the medulla and also acts on the brain

- Reduce the total peripheral resistance
- Has no effect of rennin system so can be used in case of renal failure
- Adverse effects ; postural hypotension, nasal congestion, drowsiness, dizziness, depression, liver damage, auto immune haemolytic anaemia,
- It is safe during pregnancy

B. Clonidine

- Similar in action to methyldopa

- Adverse effects include, sedation, drowsiness, dry mouth, nausea, vomiting, impotence
- Withdrawal cause rebound hypertension, due to increase sympathetic activity, s withdrawal should be gradual
- Usually given in combination with other drugs as diuretics or beta blockers

8. Vasodilators:

Hydralazine

- Directly acting smooth muscle relaxant causes vasodilatation
- Act mainly on the arteries while veins are little affected
- Adverse effects include; reflex tachycardia, headache, flushing, fluid pretension and systemic lupus erythymatosus like syndrome. This is more common in slow acetylators, who metabolized the drug slowly
- Can be given i.v for rapid reduction of BP
- Usually given with Beta-blockers to reduce the associated reflex tachycardia.

Minoxidil

- Is a potent vasodilator
- acts by potassium channels activation and increase intracellular potassium, which lead to relaxation of vascular smooth muscles
- It is mainly used in resistant and severe hypertension
- Adverse effects include, reflex tachycardia, headache, nasal congestion, salt and water retention, so should be combine with diuretics
- may cause excessive hair growth with elongation and thickening and enhance hair pigmentation(undesirable side effect specially in females), but this is utilized in the treatment of alopecia

Diazoxide

- Is a directly acting vasodilator which causes relaxation of arterial smooth muscles
- Acts by activation of potassium channels
- It cause reflex tachycardia
- Given i.v in the treatment of hypertensive emergencies as malignant hypertension, hypertensive encephalopathy and eclampsia
- Can be given in combination with beta blockers to reduce the tachycardia and diuretics to reduce fluid retention
- Also can inhibit insulin secretion by the β-cells of the pancreas, and this may be used in the treatment of hypoglycemia due to pancreatic tumors
- Adverse effects: reflex tachycardia, salt and water retention

Sodium nitroprusside

- Is directly acting vasodilator
- Used by i.v infusion for rapid reduction of the blood pressure in hypertensive emergencies
- Acts by increasing cyclic GMP and increase NO inside the cell
- It dilates both the veins and the arteries
- Produce rapid lowering of the blood pressure(30sec) but the action is short and last only for 2-3 minutes, so it is given by i.v infusion
- Adverse effects include hypotension, nausea, vomiting and headache
- Metabolised by the liver into thiocyanate , which may accumulates after prolonged use lead to cyanide toxicity

Reserpine

- Deplete neurons of catecholamines
- So reduce both cardiac output and peripheral resistance

- Adverse effects include postural hypotension, excess sedation, severe depression, Parkinson's like (reduce dopamine).

Emergency lowering of blood pressure

- The following can be used for rapid lowering of the blood pressure in case of malignant hypertension or hypertensive encephalopathy
- Oral: clonidine, ACEIs, labetalol
- Sublingual : nifedipine, glyceryltrinitrate
- I.V: sodium nitroprusside, diazoxide, hydralazine, glyceryltrinitrate, furosemide

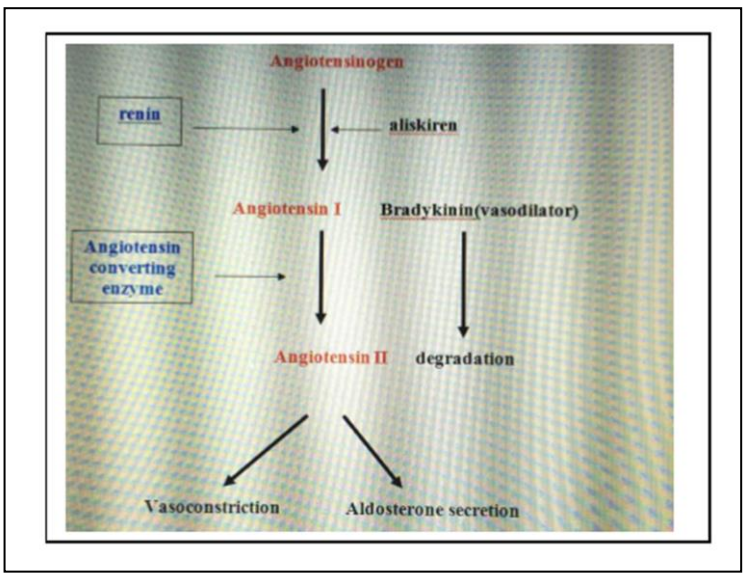
Drugs induced hypertension:

The following drugs can induces high blood pressure:

1. Non-steroidal anti-inflammatory drugs
2. Corticosteroids
3. Sympathomimetic drugs
4. Contraceptive tablets

Non-pharmacological lowering of blood pressure

- Stop smoking
- Reduce the intake of alcohol and caffeine
- Exercise
- Weight reduction
- Low salt intake
- Avoid drugs aggravating hypertension as NSAIDS, corticosteroids, MAOIs.



28. Cardiac Arrhythmias and antiarrhythmic drugs

There are basically two types of cardiac tissues:

a. atrial and ventricular muscle

b. conducting tissue (automaticity)

SA node: 70 discharge/min.

AV node: 45 discharge /min.

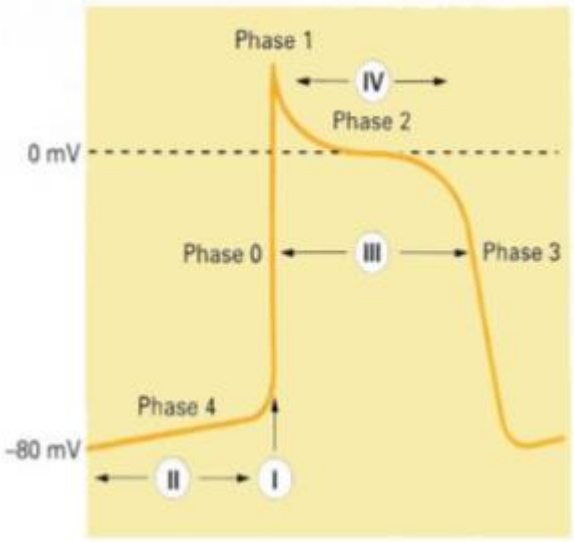
A. Overwiew: action potential of the heart

Action potential of the heart depends on ionic movement into and out of cardiac cells in resting state; the interior of the cells (whether conducting or contracting type of cells) are electronegative.

Phases of cardiac cycle:

Phase 0: is due to rapid depolarization of the cell membrane which is due to **rapid influx of Na**.

Phase1: short initial repolarization due to **outflow of K^+**



Phase 2: delay in repolarization because of slow movement of calcium (ca^{++}) from outside to inside the cell. **Phase 3**: second period of rapid repolarization.

due to outflow of k^+. **Phase 4**: full repolarization state in which everything is back to normal.

During phase 1 and 2, the cells are in absolute refractory. In phase 3 the refractoriness is relative.

B. Classification of drugs:

Class I: sodium channel blockade. They slow the maximum rate of depolarization. It may contribute to stopping dysrhythmias by decreasing the responsiveness to excitation of cardiac cells. Class I is sub classified into 3 subclasses:

Class Ia: Drugs that lengthen action potential duration & refractoriness (Examples: **Quinidine, disopyramide and procainamide**).

Class Ib: Drugs that shorten action potential duration and refractoriness (in some tissue of the heart); examples: (**lignocaine, mexiletine, tocainide and phenytoin**).

Class Ic: Drugs that have negligible effect on action potential duration and refractoriness (**flecainide & propafenone**).

Class II: beta blockers which reduce background sympathetic tone in the heart, reduce autonomic discharge (phase 4).

Class III: lengthening of refractoriness (with-out effecting sodium (Na^+) inflow in phase (0), prolongation of cellular refractoriness: example of phase III is amiodarone, bretylium, and sotalol and dofetilide

Class IV: they slow inward calcium (Ca^{++}) current (phase 2) and prolong conduction and refractoriness particularly in the SA and AV node. This explains the effectiveness of this class in terminating supraventricular tachycardia (SVT) (e.g. of drugs: **verapamil and diltiazem**).

C. Principal drugs:

1. Class I

i. Class Ia:

A. Disopyramide: This drug has significant antimuscarinic and negative inotropic effects more than quinidine or procainamide; this may result in reduction of myocardial contractility and cardiac output.

Clinical uses:

1. both for ventricular (after myocardial infarction) dysrhythmias

2. supraventricular dysrhythmias

3. it may be used in supraventricular tachycardia of the **Wolf-Parkinson White syndrome**.

Adverse reactions

1. Antimuscarinic activity leading to dry mouth blurred vision, glaucoma, and retention of urine.
2. GIT symptoms, skin rash, agranulocytosis
3. Cardiovascular: hypotension & heart failure

B. Quinidine is similar to disopyramide. It slightly enhances contractility of the myocardium (positive inotropic effect, Reference: P.N. Bennett, M.J. Brown 2008) and less ant muscarinic effect. In high dose it may precipitate arrhythmias which in some cases are fatal. This is the reason why quinidine may not be the drug of first choice, class IV drugs like verapamil is increasingly replacing quinidine use.

clinical uses:

1. It inhibits ectopic and ventricular arrhythmias.
2. Prevents reentry arrhythmias

Adverse effect of quinidine:

1. hypotension and cardiac failure
2. quinidine must never be used alone to treat atrial fibrillation.
3. serious ventricular tachycardia.
4. quinidine increases serum level of digoxin.
5. cinchonism.

C. Procainamide:

It is a derivative of a local anesthetic procaine; it is well absorbed after oral administration and has a short half-life. Part of the drug is metabolized by acetylation in the liver. The N-acetyl metabolite of procainamide has class III activity.

Adverse effects:

1. Reversible systemic lupus erythematosus-like syndrome (in 30% of patients)
2. Ventricular arrhythmias
3. CNS: depression, hallucination, psychosis.

ii. **Class Ib** (sodium channel blockade with shortened refractoriness)

A. **Lignocaine** (lidocaine, xylocaine): Basically lignocaine is a local anesthetic. The action of lignocaine is manifested when the cardiac cell is depolarized or firing rapidly a case which is seen in myocardial infarction. Therefore, lidocaine is used principally for ventricular dysrhythmias after myocardial infarction. The drug has the advantage of not markedly slow A-V conduction. It is given by intravenous route because lignocaine is subjected to first pass metabolism.

Adverse effect: is uncommon but rapid iv infusion or if the patient has heart failure it causes:

1. hypotension, dizziness, blurred vision

2. slurred speech,

3. sweating, numbness,

4. confusion and convulsion.

5. It has little effect on left ventricular function.

B. **Mexiletine and tocainide**: These are similar to lignocaine but can be given **orally**, they are used for ventricular dysrhythmias (after myocardial infarction) side effects are similar to lignocaine. Tocainide has pulmonary toxicity (pulmonary fibrosis).

iii. **Class Ic**: Na^+ channel blocker with minimal effect on refractoriness.

A. **Flecainide**: flecainide slows conduction in all cardiac cells including pathways responsible for WPW syndrome. They are used for refractory ventricular arrhythmias. Safety of flecainide is under serious consideration because it may make existing arrhythmias worse and may lead to ventricular arrhythmias which resist treatment.

B. **Propafenone** this drug has in addition beta-blocking activity.

II. Class II: catecholamine blockade

Example: Propranolol, metoprolol, oxprenolol, acebutolol, labetalol.

Class II agents diminish phase 4 depolarization; decreasing automaticity, prolong A-V conduction and decreasing heart rate and myocardial contractility. These agents are useful in arrhythmias of increased sympathetic tone; they are used for atrial fibrillation and A-V nodal reentrant tachycardia. The use of catecholamine blockade is now frequent and increasing.

III. Class III: lengthening of refractoriness without Na^+-channel blockade (potassium channel blockers).

A. Amiodarone: it is the most powerful anti- arrhythmic drug available for treatment & prevention of both atrial and ventricular dysrhythmias. It contains iodine and structurally related to thyroxin. It

is the most preferable antiarrhythmic agent in patients with moderate to severe heart failure. Amiodarone prolongs effective refractory period of myocardial cells. It also blocks Beta adrenoceptors

Clinical uses

1. chronic ventricular dysrhythmias
2. atrial fibrillation
3. resistant re-entry supraventricular tachycardia associated with WPW syndrome.

Pharmacokinetics of amiodarone:

$T_{1/2}$ = 50-100 days (long half-life), volume of distribution = 70L/ kg (large volume). The drug is metabolized in the liver and eliminated in the bile.

Adverse reaction:

Amiodarone is frequently associated with a variety of toxic effects. After chronic use 50% of patients experienced serious toxic effects; these include:

1. cardiovascular: bradycardia, heart block, induction of ventricular dysrhythmias.
2. corneal micro-deposit; this leads to photophobia. These are dose related and resolve when the drug is discontinued.
3. It contains iodine and this leads to hypo- or hyperthyroidism.
4. Photosensitivity which is presented as blue discoloration of skin.
5. pulmonary fibrosis.
6. Hepatitis.
7. GIT intolerance
8. CNS: neurotoxicity, tremor, ataxia, dizziness

Drug interactions with amiodarone

It increases the concentration of digoxin when the two drugs are given together.

B. Brtylium: prevent release of noradrenaline from sympathetic nerves. It prolongs cardiac refractoriness. It is used for resistant ventricular tachycardia (after myocardial infarction). The main side effect: nausea, vomiting, hypotension, and bradycardia.

C. Dofetilide and ibutilide: They are newer potassium channel blocker; it can be used as a first line drug in persistent atrial fibrillation in patients with heart failure. Because of its proarrhythmic potentials the drug should be used by expert prescriber and should be given in the hospital.

IV. Class IV: calcium channel blockade

Verapamil and diltiazem : prolong conduction and refractoriness in the A- V node and depress the rate of discharge of the SA node. Verapamil is useful in terminating supraventricular tachycardia (SVT), but it is contraindicated in SVT associated with WPW syndrome. Verapamil and diltiazem should not be used when heart failure is present. Although nifedipine is a calcium channel blocker but it has no place in treating arrhythmias (it may worsen arrhythmias) because it lowers blood pressure and associated with reflex tachycardia.

Verapamil increases serum level of digoxin When the two drugs are given together.

V. Other antiarrhythmic Drugs

A. Digoxin: This drug is basically used for heart failure.

Mechanism of action as antiarrhythmic drug:

a. digoxin shortens the refractory period in atrial and ventricular tissues,

b. however, it prologs the refractory period and diminish conduction in Purkinje fibers.

Clinical uses of digoxin

1. atrial fibrillation due to slowing of ventricular rate chiefly by vagal stimulation.
2. Supraventricular tachycardia (SVT) but not those associated with WPW-syndrome
3. Atrial flutter.
4. Cardiac failure.

Toxic effect of digoxin:

At toxic level, digoxin causes ventricular ectopic beats, ventricular tachycardia or ventricular fibrillation.

B. Adenosine: it is an endogenous purine nucleotide which slows conduction, prolongs refractory period in A-V node and dilates coronary and peripheral arteries ($t_{1/2}$: several seconds).

Clinical uses:

Supraventricular tachycardia and in this condition it is superior to verapamil and safer.

Adverse effect of adenosine:

These are not serious because of the short duration of action.

1. dyspnea.
2. facial flushing
3. chest Pain
4. bradycardia

It is contraindicated in asthma, second or third degree A-V block or sick sinus syndrome.

29. Drugs in hyperlipidemia

Lipids are carried in special macromolecular complexes termed as

LIPOPROTEINS

There are 3 types of plasma lipoprotein fractions:

1. LDL-beta-lipoprotein

2. VLDL-pre beta-lipoprotein

3. HDL-alpha-lipoprotein

Pathophysiology

The normal function of lipoproteins is to distribute and recycle cholesterol.

*Cholesterol within cells is needed for membrane growth and repair.

*Cholesterol in liver is needed to form bile acids.

*HDL takes cholesterol from peripheral cells to the liver, so it is protective against ischemic heart diseases (IHD).

Note: HDL levels are increased by:

-exercise

-weight loss

-in those living on fish diet

Hyperlipidemia

Can be:

1. Primary- due to diet and genetics

2. Secondary-is a consequence of other conditions like DM, alcoholism, nephrotic syndrome, chronic renal failure, hypothyroidism, liver disease, administration of drugs (tamoxifen, ciclosporin, thiazide diuretics, contraceptive pills, glucocorticoids, β-blockers).

Management of hyperlipidemia

*Long term decisions on management should be initiated only on the basis at least two fasting blood samples.

Management may proceed as follows:

1. *Any medical disorder* that may be causing hyperlipidemia should be treated first.

2. *Dietary adjustment*

*****Overweight patients should reduce their total caloric intake

*****Decrease alcohol intake

*****Decrease total fat intake especially of animal origin

***** Decrease carbohydrate intake, sucrose and other simple sugar intake which increases VLDL

* Excess egg yolk should be avoided

* Supplementation of fat soluble vitamins can be given

3. *Drugs*

*****Diet is necessary adjunct to drug therapy and should be continued for achievement of the full potential of drug regimen.

*****The decision to use lipid-lowering drugs is made on the basis of the overall absolute coronary heart disease (CHD) risk e.g. evidence of existing CHD, hypertension, diabetes mellitus, positive family history.

I. STATINS

e.g. simvastatin (zocor), fluvastatin (lescol), pravastatin (lipostat) are short acting

atorvastatin (Lipitor) and rosuvastatin (crestor) are long lasting inhibitors.

Mechanism of action

1. These agents block the rate limiting enzyme for endogenous hepatic cholesterol synthesis, hydroxymethylglutaryl coenzyme A (HMGCoA) reductase; this results in increased synthesis of LDL receptors (up-regulation) in the liver and increased clearance of LDL from circulation, plasma total cholesterol and LDL cholesterol fall, with a maximum effect after 1 month of therapy.
2. They also elevate HDL cholesterol
3. They have actions on the inflammatory components of atheroma progression.

All these will reduce the risk of cardiovascular events in patients with coronary artery disease.

Statins are well absorbed after oral administration, and they are metabolized in the liver.

*Short acting statins are given by mouth at night to decrease peak cholesterol synthesis in early morning.

Adverse effects are well tolerated

Headache, rash, dyspepsia, flatulence, constipation, abdominal pain, minor abnormality of liver function tests, asymptomatic elevation of muscle enzymes and myositis occurs rarely.

II. FIBRIC ACID DERIVATIVES (Fibrates)

e.g. gembfibrozil (lopid), fenofibrate, bezafibrate (bezalip), ciprofibrate

These drugs increase oxidation of fatty acids in liver and muscles. In liver, secretion of TG-rich lipoproteins falls, and in muscle the activity of lipoprotein lipase and fatty acid uptake from plasma are both increased. So plasma TG declines by 20-30% and cholesterol by 10-15%.

*There is also rise in protective HDL-cholesterol which may contribute to the reduction in non-fatal myocardial infarction.

These drugs are well absorbed from GIT, extensively bound to plasma proteins and are excreted mainly by kidney as unchanged drug or metabolites.

*They are drugs of choice for **mixed hyperlipidemia** (elevated cholesterol and TG), but may be used in hypercholesterolemia, alone or with anion exchange resins or statins (with care)

Adverse effects

1. GIT disturbances (nausea, abdominal pain, diarrhea)
2. Gall stone formation
3. Hepatotoxicity
4. Rarely myositis

III. ANION EXCHANGE RESINS (Bile acid sequestrants)

Cholestyramine (Questran)

Acts by binding bile acids in intestine, so inhibits the re-absorption of bile salts into their enterohepatic cycle, so bile acids are lost in feces.

The depletion of bile acid pool will stimulate conversion of cholesterol to bile acids, so plasma LDL-cholesterol falls by 20-25%.

It is used in hypercholesterolemia but not hypertriglyceridemia

Adverse effects

GIT side effects including constipation, abdominal fullness, anorexia and occasionally diarrhea.

IV. Ezetimibe (Ezetrol)

Selectively blocks intestinal absorption of cholesterol, leading to decrease in delivery of intestinal cholesterol to the liver. This causes reduction of hepatic cholesterol stores and increase in clearance of cholesterol from blood.

*It deceases LDL, TG and increases HDL.

***Simvastatin and Ezetimibe** in one formulation is more effective than simvastatin alone

V. NICOTINIC ACID & DERIVATIVES (Niacin or vitaminB3)

Acts as antilipolytic agent in adipose tissue, reducing the supply of free fatty acids and hence the availability of substrate for hepatic TG synthesis and the secretion of VLDL. So it lowers plasma TG and cholesterol concentrations and raises HDL-cholesterol.

***is used in **all types of hyperlipoproteinemia**

***oral dose is 100 times more than normal human nutritional needs.

Adverse effects

1. GIT upset (nausea, dyspepsia, abdominal pain, diarrhea)
2. pruritis and flushing of face, neck and ears
3. hepatotoxicity
4. gouty arthritis and hyperglycemia

*Its use is limited because of unpleasant side effects

VI. OTHER DRUGS

a. **Omega-3 marine triglycerides (Maxepa)**
   Is derived from fish oil, taken for coronary heart disease prevention (benefit may be due to antithrombotic effect).
b. **Orlistat (Xenical)** is a weight-reducing agent, lowers the glycemia in diabetes mellitus, and improves hyperlipidemia.
c. **Alpha-tocopherol acetate (vitamin E)**

Has no effect on lipid levels but is a powerful antioxidant and may have a role in prevention of atheroma (oxidation of LDL is an essential step in development of atheroma).

30. Drugs used in heart failure

Heart failure: the cardiac output is insufficient to adequately perfuse the tissue

Preload: is the cardiac filling pressure of the left ventricle (volume)

Afterload: the resistance made by the blood vessels

Drugs useful in heart failure can be classified according to their therapeutic effect into:

1. Drugs that reduce the preload; diuretics, ACEIs, nitrates
2. Drugs that reduce the afterload; angiotensin converting enzyme inhibitors (ACEIs), hydralazine
3. Drugs that increase the force of cardiac contractions (positive inotropic drugs); cardiac glycosides, phosphodiesterase inhibitors (PDIs)
4. Other drugs as dopamine, dobutamine and isoprotrenol , especially useful in improving renal blood flow in acute heart failure

Cardiac glycosides Include digoxin, digitoxin are extract of the plant called foxglove

Digoxin

Mechanism of action

- Inhibits the membrane Na^+ /K^+ -ATPase pump which is responsible for the Na^+/K^+ exchange across the cell membrane, this lead to increase intracellular Na^+
- The increase of intracellular Na^+ lead to increase of intracellular Ca^{++} that increase the force of myocardial contraction

- The increase in intracellular Ca^{+} occurs because reduce extrusion of Ca^{+} by the Na^{+}/Ca^{++} exchange mechanism
- Increase in vagal activity (cholinomimetic effect); this lead to slow heart rate, slow atrial conduction and prolonged refractory period of AV node
- Potassium ions antagonise digoxin action and calcium ions potentiates its action

Pharmacokinetics

1. absorbed well from GIT, it is lipid soluble
2. low protein binding (20-30%)
3. mainly excreted unchanged by the kidneys
4. has narrow therapeutic index, therapeutic serum levels (1-2ng/ml)

Clinical uses

1. congestive cardiac failure
2. atrial fibrillation

Adverse effects

- GIT nausea, vomiting and diarrhea due to effect on smooth muscles and CTZ
- Cardiac arrhythmias and conduction defect
- CNS; weakness, dizziness, fatigue, confusion, visual disturbances and psychosis
- Gynaecomastia and skin rashes

Drugs Interaction with digoxin

- Diuretic cause hypokalemia which aggravate digoxin toxicity
- Quinidine displace digoxin from tissue binding and increase toxicity

Angiotensin converting enzymes inhibitors :as Captopril, enalapril and lisinopril

- Inhibit ACE so inhibits conversion of angiotensin I to angiotensin II so lead to vasodilatation (arterial and venous) so reduce both preload and afterload
- Reduce aldosterone release (increase Na+ and water excretion), so reduce blood volume and venous return to the heart
- Angiotensin receptors antagonists as losartan and valsartan has similar effects and can be used instead of ACEIs if adverse effects occur

Diuretics in heart failure:

Include the thiazides loop and potassium sparing diuretics

- Increase sodium and water excretion useful in oedema and dyspnea of heart failure and reduce the preload
- In mild heart failure usually thiazides diuretics are used, while in sever heart failure loop diuretics are preferred as furosemide
- Potassium sparing diuretic as triamterene, can be used alone or in combination with loop or thiazides diuretics
- All the diuretic are useful in the treatment of chronic heart failure
- Loop diuretic as furosemide are also useful in the treatment of acute heart failure

Vasodilators in heart failure

- Nitrates acts mainly by reducing the preload of the heart, they are mainly venodiators so reduce the venous return to the heart. Nitroglycerine is used in acute heart failure given by injection or sublingually, isosorbide dinitrate may be used orally in chronic heart failure, but tolerance might occur
- Hydralazine is a directly acting vasodilator used in chronic heart failure
- Sodium nitroprusside is used in cases of acute heart failure

- α-blockers as prazosin and doxazosin can also be used in chronic heart failure
- All vasodilators can cause tachycardia which might affect the control of heart failure

β-Blockers in heart failure

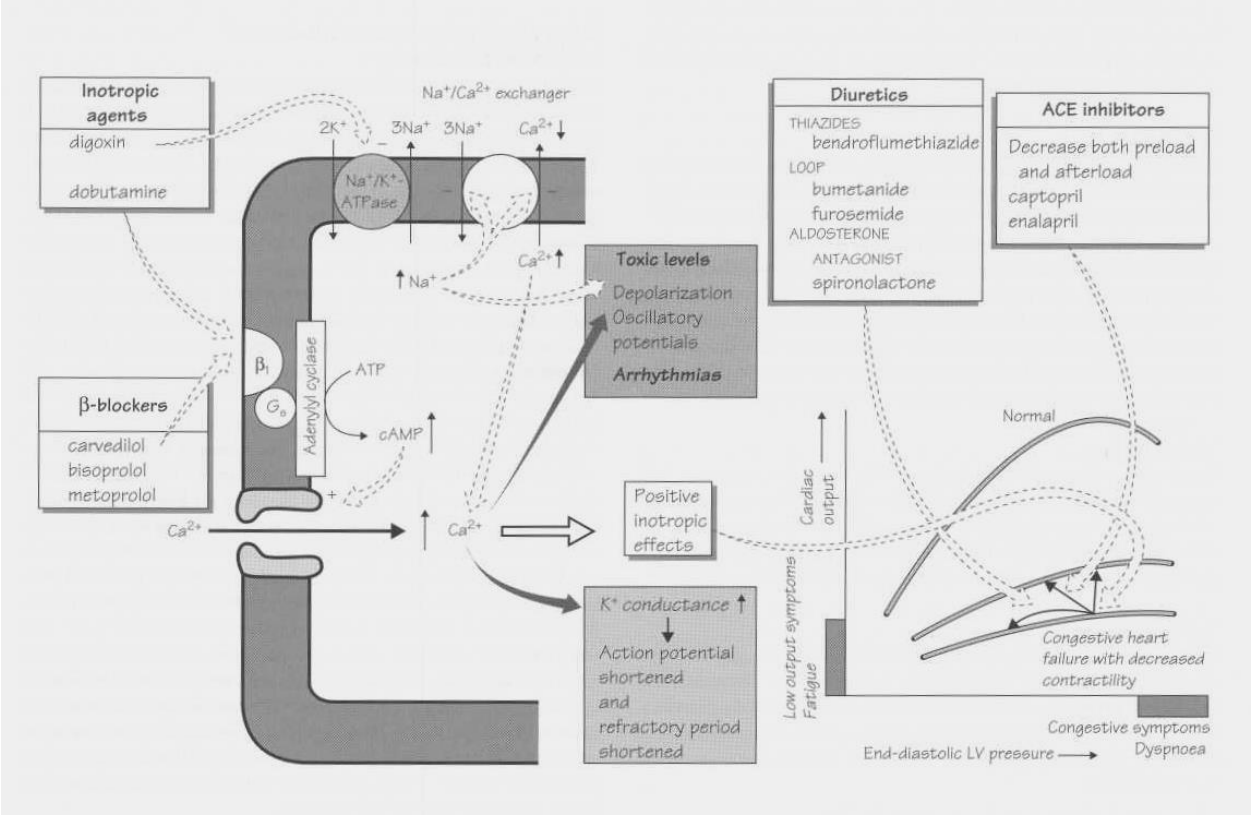
- β-blockers decrease myocardial contractility and worsen heart failure
- Long term use of some β–blockers was shown to improve survival in heart failure by blocking the overactive sympathetic activity
- Commonly used –blockers include carvedilol, bisoprolol and metoprolol

Other drugs in heart failure

- Phosphodiesterase inhibitors as amrinone, increase cAMP and stimulate the heart also has peripheral vasodilator action. They are not found to be effective in the long term treatment of heart failure
- Dopamine and dobutamine has positive inotropic effect (β1)and renal vasodilators (β2 & dopamine) used only in acute heart failure as they have to be given by i.v infusion
- Theophylline is a phosphodiesterase inhibitor which has a positive inotropic effect on the heart in addition to its bronchodilator effect which might be useful in acute heart failure

Drugs useful in acute left ventricular failure (pulmonary oedema)

- Is a medical emergency that require rapid treatment
- Loop diuretic as furosemide is given intravenously
- Morphine is useful when given i.v, i.m of s.c, it relief anxiety and reduce the tachypnoea and might dilate the pulmonary vessels
- Vasodilators as nitrates i.v or sodium nitroprusside and hydralazine might be useful


Inotropic agents
digoxin
dobutamine
Na+/Ca2+ exchanger
2K+
3Na+
3Na+
Ca2+
Na+/K+-ATPase
↑Na+
Ca2+↑
Toxic levels
Depolarization
Oscillatory potentials
Arrhythmias
Diuretics
THIAZIDES
bendroflumethiazide
LOOP
bumetanide
furosemide
ALDOSTERONE ANTAGONIST
spironolactone
ACE inhibitors
Decrease both preload and afterload
captopril
enalapril
β-blockers
carvedilol
bisoprolol
metoprolol
β1
Gs
Adenylyl cyclase
ATP
cAMP
Ca2+
Ca2+
Positive inotropic effects
K+ conductance ↑
Action potential shortened and refractory period shortened
Normal
Cardiac output
Low output symptoms
Fatigue
Congestive heart failure with decreased contractility
Congestive symptoms
Dyspnoea
End-diastolic LV pressure

31. Drugs in Thromboembolic Disorders

Thrombosis is a pathological condition results in formation of clots despite absence of bleeding.

A. **Anticoagulants]**

Prevent the development and propagation of thrombi by disrupting the coagulation cascade and suppress production of fibrin. They are more effective *in venous thrombi because these are mainly composed of fibrin*.

Injectable anticoagulants

a. Heparin (unfractionated heparin) (UFH)

b. Low molecular weight heparins (LMWHs) ex. enoxaparin

c. Direct inhibitors of thrombin ex. Lepirudin

d. LMW heparinoids ex. danaparoid

	UFH	LMWHs
structure	Large molecule - sulphated mucopolysaccharides containing fractions varying in molecular weights between 6000-25,000	Smaller molecule - contain only the low molecular weight fractions of heparin
Mechanism of action	Heparin has fast anti-coagulant effect. It binds to antithrombin III and increasing the rate of its inactivating effect on thrombin and of activated factor X (Xa). This prevents formation of blood clots.	Fast effect bind to antithrombin and increasing the rate of its inactivating effect on factor Xa

PKS:		
Routes of administration	it is not absorbed from GIT as it is polar due to its strong negative charges and given (i.v.) or (s.c.)	Injected i.v. or s.c.
Elimination kinetics	It binds to several plasma proteins and to sites on endothelial cells and some is excreted by kidney. Due to these, elimination of heparin involves a combination of zero-order and first-order kinetics, the effect of which is the plasma biological effect t1/2 (biological t1/2) alters disproportionally with dose. Heparin administration Requires hospital admission and dose needs to be adjusted by monitoring patient's activated partial thromboplastin time (APTT), to avoid bleeding due to overdose. The optimum therapeutic range of APTT is 1.5 – 2.5 times the pretreatment level	are less protein bound and have a Predictable dose-response profile and fixed t1/2. Dose can be administered according to body weight at home or in out-patient without monitoring of APTT
Duration of action	short (6)hours ; necessitates frequent injections	Longer, require once-daily administration
Safety during pregnancy	Safe as it cannot pass the placental membrane due	safe

	to its polarity.	
Main side effects	1)bleeding 2)Heparin-induced thrombocytopenia (HIT) characterized by arterial thrombosis and bleeding 3) dose-related Osteoporosis on several months use; mostly seen during pregnancy	Less incidence of HIT and osteoporosis
Antidote(if bleeding occur due to overdose)	Protamine sulphate: a positively charged basic protein, given i.v. Can bind heparin forming an inactive complex that is excreted.	Effectiveness of protamine sulphate is unknown
Uses	1- acute deep venous thrombosis (DVT) and pulmonary embolism 2- prevention of Postoperative DVT and pulmonary embolism in high risk patients i.e. after major abdominal surgery 3-DVT and pulmonary embolism during pregnancy 4 – Prevention of thrombi in Unstable angina and acute myocardial infarction. 5-prevention of clotting in blood samples for laboratory tests as it can prevent clotting in vitro.	Same uses

Direct inhibitors of thrombin: - ex.
Lepirudin:

Inhibits thrombin, by forming irreversible complex with it that is excreted by kidney.

Use: prevents thrombosis in patient gets HIT.

LMW heparinoid ex.

danaparoid: similar mechanism of action and kinetics to LMWHs but contain heparin molecule from animal source.

Oral anticoagulants

a. Coumarins ex. Warfarin
b. Indandiones ex. phenindione is obsolete because of their allergic toxic effects.

WARFARIN:

Mechanism of action:

In live, gamma-carboxylation of factors II, VII, IX and X is important for activation of these factors. During this process, active (reduced) vitamin K act as a co-factor and is oxidized to an inactive epoxide and must be reduced by the enzyme vitamin K epoxide reductase to become active again. Warfarin is structurally similar to vitamin K and competitively inhibits epoxide reductase, so limiting availability of the active form of the vitamin to form coagulant factors. The overall result is a shift in haemostatic balance in favor of anticoagulation because of the accumulation of clotting factors with absent or decreased gamma-carboxylation sites. Due to this indirect mode of action, anticoagulation is delayed until the functioning clotting factors already present in the circulation have been eliminated; the net result is that anticoagulant protection is not effective until about 72h after the first dose.

If a rapid anticoagulation is required i.e. acute DVT an initial dose of heparin or LMWH should be used with warfarin for the first 3 days.

The anticoagulant effect also continues for 72 hours after drug discontinuation till the non-functioning clotting factors are eliminated.

Pharmacokinetics:

- Plasma protein binding = 99%; clinical significance: Drugs as Sulphonamides that displace warfarin from plasma protein binding sites can increase the anticoagulant effect. Because the anticoagulant effect of warfarin is directly related to the plasma concentration, bleeding may occur unless warfarin dose is reduced.
- Metabolism: warfarin is readily absorbed from the GI tract. It is metabolized by hepatic CP450; enzyme inhibitors as cimetidine, metronidazole, and chloramphenicol can increase warfarin plasma concentration and the anticoagulant effect. Bleeding can occur unless warfarin dose is reduced.
- On the contrary, enzyme inducers as carbamazepine, rifampicin can reduce the anticoagulant effect, thrombosis may occur unless the dose of warfarin is increased.

Broad spectrum antibiotics eliminate the intestinal flora that Synthesize vitamin K and can potentiate the anticoagulant effect of warfarin.

Dose monitoring:

is by assessing INR (international normalized ratio), which is estimated from patient's prothrombin time.

Uses: because it can be given orally so it is used for

- **Long term** treatment and prevention of :

1. DVT and pulmonary embolism.
2. thromboembolism associated with prosthetic heart valves
3. thromboembolism associated with atrial fibrillation.

4. thromboembolism following myocardial infarction.

Side Effects:

1. Bleeding

Reversal of anticoagulant effect (antidote for overdose): vitamin K_1

2. skin necrosis and ecchymosis
3. **teratogenic:** contraindicated during pregnancy as it crosses the placenta and can cause congenital malformation an increase in the chance for hemorrhage in both the baby and mother.

Contraindications of anticoagulant drugs: in conditions which there is a tendency to bleed such:

1-Haemophilia 2-Thrombocytopenia 3-Severe hypertension 4- Intracranial hemorrhage 5-active peptic ulcer, esophageal varices and ulcerative colitis 6- Renal or hepatic Impairment 7- Recent surgery to the brain, spinal cord, or eye 8- warfarin during pregnancy and conditions that disrupt hepatic synthesis of clotting factors as liver disease and alcoholism.

B- Fibrinolytics, thrombolytics

Mechanism of action**:** They dissolve thrombi by activating plasminogen leading to formation of plasmin, a proteolytic enzyme that breaks the insoluble fibrin (the framework of thrombi) to soluble fibrin products.

Examples:

Alteplase:	**Streptokinase**:
a tissue plasminogen activator obtained by rDNA technology	Obtained from streptococci
-specifically activates plasminogen that binds to fibrin in the clot so plasmin is formed and dissolve fibrin locally. -has no effect on circulating plasminogen and less likely to cause	-binds to circulating plasminogen to form an activator complex which then causes conversion of other plasminogen molecules to plasmin. -Because of this it can cause systemic circulation disturbance

systemic coagulation disturbance. It can dissolves aging and resistant thrombi	and bleeding.
given IV	also
Uses: 1-acute myocardial infarction 2-DVT 3- pulmonary embolism 4- Ischemic stroke 5- peripheral arterial thrombosis	Same uses
Side effects: 1-Bleeding 2-microemboli due to disintegration of thrombus.	Same side effects in addition to hypotension and allergic reactions due to ant streptococcal antibodies.
Antidote :Tranexamic acid	same

C. Antiplatelets

Prevent platelets aggregation. They are used in prophylaxis of arterial thrombosis because these are mainly composed of platelets.

- **Aspirin low dose** :(80-325 mg/day) inhibits platelets aggregation by Inhibiting the synthesis of TXA_2 due to irreversible acetylation of cyclooxygenase.
- **Clopidogrel:** inhibits platelets'ADP receptors that are involved in binding of platelets to fibrinogen and to each other. It is given once daily orally and antiplatelets effect lasts 7-10 days
- **Abciximab**: monoclonal antibody that blocks platelet GP IIb/III receptors that is involved in the final step binding of platelets binding to fibrinogen .
- **Dipyridamole**: inhibits phosphodiesterase enzyme, so increased platelet c AMP which inhibits platelet aggregation.
- **Epoprostenol (prostacyclin):** stimulates adenylcyclase enzyme, thereby increased cAMP formation which inhibits platelet aggregation.

Uses:

1. prevention of M.I in patient with atherosclerosis or unstable angina.
2. prevention of recurrence of MI.
3. cerebral ischemic attacks
4. atrial fibrillation
5. coronary artery grafting

Drugs used to control bleeding

Tranexamic acid

Mechanism of action: competitively inhibits binding of plasminogen to tissue plasminogen activator so prevents conversion of plasminogen to plasmin, thus prevents fibrinolysis .

Uses: Bleeding *due to*

1-overdose of fibrinolytics 2- thrombocytopenia 3-haemophilia 4- prevention of hyperplasminaemic bleeding that results from damage to tissues rich in plasminogen activators i.e. after prostatic surgery, tonsillectomy, uterine cervical biopsy , menorrhagia and bleeding due to intrauterine contraceptive device

Vitamin K preparations:

Vitamin K1: is a fat soluble vitamin, requires bile salt for absorption if given orally

and can be given I.M, S.C and I.V.

Rapid intravenous injection cause anaphylactic reactions with dyspnea, chest tightness, back pain and even death.

Uses: 1.Dietary vitamin K deficiency 2. haemorrhagic diseases of newborns

3. warfarin overdose . It Stops bleeding in 12 h.

Vitamin K3 (menadiol): is a water soluble synthetic analogue, and takes 24 hours to act, but its effect lasts several days, can be given orally, I.M, and I.V.

Use:hypoprothrombinaemia due to malabsorption

Side effects: haemolytic anaemia in G6PD deficient patients and neonates.

32. Hematinic Drugs

Iron Therapy, Vitamin B12, Folic acid and Others

Iron

- Hemoglobin contains more than two-thirds of total body iron
- Iron stores represent about one-third of body iron (stored as: ferritin, a water-soluble protein-iron complex, and hemosiderin, an insoluble aggregates in liver, marrow, spleen and muscles)
- Normal human absorbs only 5-10% of iron in the diet; i.e. 0.5-1 mg/day (average diet in Europe contains 5-10 mg iron/day) (Average daily iron loss is 1 mg in feces and desquamation of skin).
- Iron deficient or pregnant woman absorbs about 30% of dietary iron (up to 3 mg/day)
- Menstrual loss is about 10-15mg/period
- Iron is absorbed mainly in duodenum
- Ferrous iron is more readily absorbed than ferric. Ingestion of a reducing agent such as ascorbic acid increases ferrous form.
- Food reduces iron absorption due to chelation by phytates, tannates and phosphates
- Control of iron balance in the body is achieved by regulation of absorption; when stores decline, absorption increase and vice versa
- Excess iron in the body cannot be excreted and can accumulate
- Prolonged heavy excess of iron intake can result in hemosiderosis (deposition of hemosiderin inside the cells e.g. heart and liver)

Iron Therapy

- Is indicated for prevention or cure of iron deficiency
- Oral therapy is the treatment of choice for almost all patients due to their efficacy, safety and low cost.
- 200mg ferrous sulfate (containing 60mg elemental iron) three times daily can raise hemoglobin by 1g/dL in the first week and 2g/dL after 3 weeks.

Oral Iron therapy

- In iron deficiency, it is assumed that about 30% of iron will be absorbed from GIT
- Iron stores are less easily replenished by oral therapy than by injection. That is why oral therapy (at lower doses) should be continued for 3-6 months after Hb concentration returned to normal

Iron therapy is needed in:

1. Iron deficiency (dietary lack or chronic blood loss)
2. Pregnancy (fetus takes iron from the mother even if she is iron deficient)(iron and folic acid are given from the 4^{th} month of pregnancy)
3. Abnormalities of the GIT e.g. malabsorption syndromes
4. Premature babies (low iron stores) and in babies weaned late (very little iron in human milk and even less in natural cow's milk)

Liquid formulations are available for adults and for small children but they stain the teeth.

The ratio of elemental iron to the total strength of iron salt tablet

Preparation	Tablet	Elemental Iron /tablet	Ratio
Ferrous sulfate	200mg	67mg	1 in 3

Ferrous gluconate	300mg	35mg	1 in 9
Ferrous fumerate	200mg	65mg	1 in 3

Adverse effects

10-20% of patients have symptoms, generally, GI upset (dose-related): nausea, abdominal pain, either constipation or diarrhea

Oral iron blackens the feces.

These side effects can be reduced by:

- taking tablets with food
- reducing the dose,
- using divided doses,
- taking alternative iron salt

Reduction of GI disturbances is important to ensure compliance

Interactions with iron

- Iron chelates in the gut with several drugs and reduce their absorption e.g. tetracyclines, ciprofloxacin, methyldopa, levodopa, and carbidopa
- It forms stable complexes with thyroxine, captopril, and bisphosphonates and also reduces their absorption.

(Ingestion should be separated by a minimum of 2 hours).

Parenteral iron therapy

May be required if:

- iron cannot be absorbed from the intestine
- the patient cannot be relied on to take it or experience intolerable GI symptoms
- if there is continuing blood loss

The speed of hemopoietic response is not quicker than that with full doses of oral iron, but injectable iron is stored better

than oral iron and is utilised over months

Parenteral Iron Preparations

Iron dextran: a complex of ferric hydroxide with dextran (given by deep i.m. injection into the gluteal muscle, or by slow i.v. injection or by infusion)

Iron sucrose: a complex of ferric hydroxide with sucrose (given by slow i.v. injection or by infusion)

Oral iron therapy should not be given 24 hours before and for 5 days after the last parenteral injection of iron (to avoid saturating transferrin binding capacity which results in high unbound plasma iron concentration)

Adverse effects of parenteral Iron

- May cause immediate and severe anaphylactoid reactions, fever, and arthropathy (patients should be given small dose initially)
- may unmask folic acid deficiency because of increased hemopoiesis

General reactions: headache, dizziness, nausea, vomiting, hypotension, pressure sensation in the chest, metallic taste, urticaria ... The intramuscular injection is painful and may permanently stain the skin.

Contraindications to iron therapy

- Not given for anemia of chronic infection (where utilization of iron from stores is impaired)
- Not given in hemolytic anemias (e.g. sickle cell anemia) as iron from hemolysed cells, remains in the body, and also increased hemopoiesis stimulates increased iron absorption.

- A history of allergic disorders including asthma, eczema and anaphylaxis is a contraindication to parenteral iron.

Acute overdose: poisoning

- Orally, can cause severe GI irritation and necrosis of the mucous membranes
- Is particularly dangerous in children (causes metabolic acidosis)

Chronic iron overload

- Humans are unable to excrete excess iron, and accumulation occurs.
- Excessive parenteral iron therapy or a large number of blood transfusions (e.g. in thalassemia) can lead to hemosiderosis. Oral iron over many years has also been reported to cause hemosiderosis.

Iron chelating agents

Parenteral iron chelator: Desferrioxamine

Oral iron chelators: Deferiprone, Deferasirox

Desferrioxamine (Deferoxamine)

- Is a parenteral iron chelating agent forming a non-toxic complex with ferric iron
- This complex (ferrioxamine or feroxamine) is stable which is excreted in urine (which becomes pink in color), and also in bile
- Not absorbed from the GIT
- Has negligible affinity for other metals
- With chronic use, cataract, retinal damage and deafness can occur, hypotension may result if infused rapidly

Oral iron chelators

Deferiprone

- absorbed in the upper GIT and mainly excreted via the kidney
- less effective than desferrioxamine
- carries the risk of arthropathy, neutropenia and agranulocytosis
- useful alternative for patients unable to tolerate desferrioxamine

Deferasirox

Binds selectively to ferric iron

Provides 24 h chelation with once daily

Effective in removing cellular and serum iron and excrete it in feces

Side effects: GI disturbances, skin rash, cytopenias, and increased creatinine level.

Vitamin B12 (cobalamins)

- is an active cellular coenzyme
- essential for demethylation of tetra-hydrofolate and thus for DNA and RNA synthesis
- animal protein (meat) is the major dietary source in man
- in presence of the intrinsic factor (a glycoprotein secreted by the parietal cells of the fundus and cardia) ~70% of ingested cobalamin is absorbed via receptors in the ileum (<2% in its absence)

- Daily requirement is 3 microgram
- Absorption mainly in the terminal ileum
- Cobalamin is not significantly metabolized. It passes into bile (with enterohepatic circulation) and excreted via the kidney

- Body stores amount to about 5 mg mainly in the liver and are sufficient for 2-4 years.

Deficiency of vitamin B12 in the body leads to:

Megaloblastic anemia

Degeneration of the brain, spinal cord (subacute combined degeneration) and peripheral nerve.

Abnormalities of epithelial tissues, particularly of alimentary tract e.g. sore tongue and malabsorption

Indications

- Pernicious anemia: atrophic gastric mucosa is unable to produce intrinsic factor (and acid) with failure to absorb vitamin B12
- Malabsorption syndromes

Preparations and use

- Hydorxocobalamin is preferred. It binds to plasma proteins to a greater extent than cyanocobalamin i.e. Less free to be excreted in urine. Therefore, it is effective at lower doses and for longer interval.
- Initial stimulation of hemoglobin synthesis often depletes iron and folic stores. Thus, supplements of these may be needed.
- Hypokalemia may occur at the height of the erythrocyte response due to uptake of potassium by rapidly increased erythrocyte mass

Adverse effects

- Virtually do not occur. The use of vitamin B12 as a tonic may obscure the diagnosis of pernicious anemia
  - Folic acid**, if used alone** (because of incorrect diagnosis of the megaloblastic anemia due to folic acid deficiency), it may accelerate progression of subacute combined degeneration of the nervous

system due to enhanced vitamin B12 deficiency resulting from increased hemopoiesis.

Folic acid (pteroylglutamic acid)

Folium = latin for a leaf (discovered in spinach leaves)

One of the B group of vitamins

Functions

- Folic acid (dihydrofolate) is activated by reducing it to tetrahydrofolic acid (by the enzyme dihydrofolate reductase).
- Tetrahydrofolic acid is important in the biosynthesis of purines and pyrimidines, which are the precursors of DNA and RNA (important in cell division).
- Tetrahydrofolic acid (the formyl derivative) is called folinic acid
- Deficiency can lead to megaloblastic anemia
- Vitamin B12 plays a role in folate metabolism (it is a co-enzyme for demethylation of THFA; thus, for DNA synthesis)
- Therefore, the megaloblastic marrow of cobalamin deficiency is partly due to interference with folic acid utilization and can be partially reversed by folic acid.

Occurrence

- Folic acid is widely distributed particularly in green vegetables, yeast and liver
- Daily requirement 50-100 µg
- Body stores last for about 4 months

Indications

It is used for deficiency of folic acid which is either due to:

- Decreased supply (common in malnutrition, alcoholics, some slimming diets, elderly ...)

- Increased requirement e.g. pregnancy, hemolytic anemias

Pregnancy

- Requirement is increased from 100µg to 300-400 µg/day.
- Vigorous iron therapy in pregnancy may unmask folate deficiency

Prevention of fetal neural tube defect

- Folic acid supplementation taken before conception and during early weeks of pregnancy can prevent the condition if occurred in a previous pregnancy

Drugs and folic acid

- Antiepileptic drugs particularly phenytoin, primidone and phenobarbitone mainly as enzyme inducers.
- Some antimalarials e.g. Pyrimethamine may interfere with conversion of folate to active tetrahydrofolate leading to macrocytic anemia
- Methotrexate another folate antagonist may cause a megaloblastic anemia

Contraindications

- **Imprecisely** diagnosed megaloblastic anemia is the principal contraindication (if due to B12 deficiency, folic acid supplementation may precipitate subacute combined degeneration of the spinal cord)
- Tumour cell proliferation in some cancers may be folate dependent and folic acid should be used in malignant disease only when there is confirmed folate deficiency anemia.

Preparations and dosage

- orally, 5 mg per day
- Usually given for 4 month
- Higher doses (15 mg) in malabsorption

- Folinic acid has no advantage on folic acid except in treatment of toxic effects of methotrexate

Erythropoietin

Erythropoietin is a glycoprotein hormone that controls red blood production (erythropoiesis). It has other functions e.g. it may have a role in neuronal injury and in wound healing.

Also called hemopoietin; it is produced mainly by the kidney (interstitial fibroblasts) and is also produced by the liver.

Uses

It is used in treating anemia resulting from chronic kidney disease and myelodysplasia, resulting from the treatment of cancer (chemotherapy and radiation).

33. Antibacterial agents: Part I

Antimicrobial is a general term can be classified according to the type of microorganisms that they act on. There are 5 groups of drugs (Laurence, 2008):

1. Antibacterial
2. Antiviral
3. Antifungal
4. Antiprotozoal
5. Anthelminthic drugs

Antimicrobial drugs can be also classified into:

1. Bacteriostatic: This results in arresting the division and multiplication of bacteria
2. Bactericidal: These types of antimicrobial drugs kill the bacteria such as penicillins, and cephalosporins.

Classification of antibacterial drugs:

1. Inhibition of cell wall synthesis: these drugs interfere with the ability of the bacteria to resist osmotic pressure so it swollen and burst. Example: **Penicillins, Cephalosporins, and vancomycin**.
2. Inhibition of protein synthesis: These drugs interfere with the synthesis of peptide chain of the ribosoms of the organisms. These include **chloramphenicol, erythromycin, and aminoglycosides**.
3. Nucleic acid inhibitors: Drugs may interfere directly with microbial DNA or its replication, an example: **quinolons, metronidazole**, or with RNA such as **rifampicin**. Indirect inhibitors of nucleic acid synthesis occur with **sulphonamides** and **trimethoprim**.

Resistance to antimicrobial agents:

(Lippincott's illustrated review, 5rd edition, 2012)

A. Genetic alterations:

Resistance develops due to:

1. the ability of DNA to undergo spontaneous mutation.

   If the microorganism survives the mutation, it may replicate and transmit properties to daughter cells, thus producing resistant strains that may proliferate. Example: Rifampicin-resistant Mycobacterium tuberculosis.

2. the ability of DNA to move from one organism to another.

   This is the commonest and most important way of transferring drug resistance. Strands of DNA that are situated at the outer surface of the chromosomes (Plasmids) may enter microorganism by phage-mediated mechanism. Plasmids contain codes (gene) capable of alteration of various metabolic enzymes such as:

   a. Beta-lactamase which splits the beta lactam ring of penicillins
   b. Enzymes that destroys aminoglycosides.

B. Altered expression of proteins in drug-resistant organisms:

1. Modification of target sites: Alteration of the target site through mutation can result in resistance. Example:

i. mutation in penicillin binding proteins (PBP) in methicillin-resistant S. aureus,

ii. decreased sensitivity of dihydrofolate reductase enzyme in organisms resistant to trimethoprim.

2. Decreased accumulation: Decreased penetrability of antibacterial agent can protect organisms against that antibiotic because it can not reach to the site of action due to the presence of either a

lipopolysaccharide layer (gram-negative bacteria) or of an efflux system that pumps out the drug (**tetracycline, primaquine**).

3. Enzymatic inactivation: The ability to destroy or inactivate the antimicrobial agent can demonstrate an example of resistance of microorganisms. The best example is the **Beta-Lactamases** which destroy many **penicillins** and **cephalosporins** and **acetyltransferase** which convert **chloramphenicol** to an inactive compound.

Classification of antibacterial drugs:

1. **Inhibition of cell wall synthesis:**

   This group of drugs has selectivity in interfering with the synthesis of the cell wall of the bacteria, the structure of which is sufficiently different from mammalian cells. The cell wall of microorganisms contains pepidoglycan (a polymer); which is joined together by transpeptidaion.

   A. Beta-Lactams
      a. penicillins
      b. Cephalosporins
      c. Carbapenem
      d. Monobactam

   B. Other inhibitors of cell wall synthesis

      Vancomycin

2. Inhibition of protein synthesis (covered by a separate lecture)
   a. aminoglycosides
   b. Tetracycline
   c. Macrolides (erythromycin, clindamycin
   d. Others (chloramphenicol)
3. Inhibition of nucleic acid synthesis: (covered by a separate lecture)

a. Sulphonamides
b. Quinolones (e.g. ciprofloxacin)
c. Azoles (e.g. metronidazole)

(Part I: is devoted for Penicillins and Cephalosporins)

I. Beta-Lactams antibiotics

A. Penicillins:

Classification of penicillins: Penicillins can be classified as follows:

1. Natural penicillins
2. Antistaphylococcal penicillins
3. Antipseudomonal penicillins: (carboxypenicillin and Ureidopenicillin)
4. Extended-spectrum penicillins: Ampicillin and Amoxicillin
5. Other Beta lactam antibacterial: Carbapenem (imipenem)

i. Natural penicillins:

1. Penicillin G (benzyl penicillin, crystalline penicillin) (for IM, IV)
2. Phenoxymethylpenicillin (for oral use)
3. Procaine Penicillin (for IM use only)
4. Benzathin Penicillin (long acting, for IM use only)

Clinical uses of natural penicillins:

1. Streptococcal infection
2. Meningococcal
3. Clostridium
4. Diphtheria
5. Anthrax
6. Syphilis
7. Bacteroides

Absorption and excretion of penicillins:

Absorption of penicillins from the GIT is mostly affected by food except (amoxicillin) and should be given 1-2 hours before or after food.

Excretion mainly unchanged in urine through glomerular filtration and active tubular secretion.

Adverse effects of penicillins:

The most common adverse effects are:

1. Hypersensitivity reaction
    a. Anaphylactic (rare)
    b. Urticaria
    c. Severe pruritus
    d. Fever
    e. Bronchospasm
2. Seizures
3. GIT: diarrhea
4. Hemolytic anemia

ii. Antistaphylococcal penicillins:

This class includes the following drugs:

1. Methicillin can be given IM or IV.
2. Nafcillin can be given Oral, IM, and IV.
3. Cloxacillin can be given Oral, IM, and IV.
4. Flucloxcacillin.
5. Oxacillin and dicloxacillin

These drugs have a narrow spectrum activity. It should be noted if the Staphylococcal infection is methicillin resistant (**M**ethicillin **r**esistant **S**taphylococcal **A**ureus (MRSA), in this case vancomycin should be used immediately.

iii. Antipseudomonal Penicillins:

Carboxypenicillins: carbenicillin, ticarcillin

Ureidopenicillins : azlocillin, piperacillin

Carbenicillin, the very first antipseudomonal carboxypenicillin, is now obsolete. The ureidopenicillins, piperacillin, mezlocillin, and azlocillin, are also active against selected gram-negative bacilli, such as *Klebsiella pneumoniae.*

Because *Pseudomonas aeruginosa* easily develops resistance, antipseudomonal penicillin is often used in combination with other antibacterial agents such as gentamicin or quinolone derivatives for pseudomonal infections.

Ticarcillin and **piperacillin**: these agents are also available combined with **clavulanic acid**, a Beta-lactamase inhibitors; This combination with Beta-lactamase inhibitor extends the activity of these penicillins to include Beta-lactamase-producing strains of *S aureus* as well as some Beta-lactamase-producing gram-negative bacteria. (*Katzung; Basic and Clinical Pharmacology, 2006, Chapter 43*).

iv. Extended-Spectrum Penicillins: Ampicillin and Amoxicillin.

These drugs have greater activity than penicillin against gram-negative bacteria because of their enhanced ability to penetrate the gram-negative outer membrane. They are inactivated by many Beta-lactamases as the case with penicillin G

Ampicillin and amoxicillin have almost similar spectrum of activity, but significant differences between the two can be recognized:

a. amoxicillin is better absorbed orally,
b. given three times daily as 250–500 mg.

While absorption of ampicillin is affected by food and given 4 times daily. These drugs showed activity when given orally to treat urinary tract infections, sinusitis, otitis, and lower respiratory tract infections. Its use to treat uncomplicated salmonella gastroenteritis is debatable because it may prolong the carrier state.

Pivampicillin and bacampicillin: These are esters of ampicillin. They are de-esterified in the intestinal mucosa or the liver to release ampicillin. This very much improves the absorption of ampicillin and improves bioavailability.

v. **Other Beta lactam antibacterial**: Carbapenems (imipenem)

(LAURENCE, CLINICAL PHARMACOLOGY, 2008)

1. Carbapenems

The carbapenems are structurally related to Beta-lactam antibiotics. imipenem and meropenem are licensed for use in the USA. Imipenem has a wide spectrum of activity to include:

a. *P. aeruginosa*,
b. Beta Lactamase producing gram-positive and negative organisms,
c. Anaerobes.

Imipenem *(half-life=* 1 h) is metabolized and inactivated in the kidney to products that are potentially tubular nephrotoxic; combining imipenem with cilastatin (This combination is called **Primaxin**), a specific inhibitor of dihydropeptidase—an enzyme which is responsible for its renal metabolism—prevents both inactivation and toxicity. Imipenem is used to treat septicemia, particularly of renal origin, intra-abdominal infection and nosocomial pneumonia.

Adverse effects. 1. gastrointestinal upset including nausea, vomiting and diarrhea, 2. blood disorders, 3. allergic reactions, 4. confusion and convulsions.

2. Monobactams

Monobactams are drugs with a monocyclic Beta-lactam ring. They are relatively resistant to Beta-lactamases and active against gram-negative rods (including pseudomonas). They have no activity against gram-positive bacteria or anaerobes. **Aztreonam** is the only monobactam available in the USA. It resembles aminoglycosides in its spectrum of activity.

Penicillin-allergic patients tolerate aztreonam without reaction. Occasional skin rashes and elevations of serum aminotransferases occur

B. Cephalosporins:

(Katzung 2006)

Cephalosporins are similar to penicillins, but more stable to many bacterial Beta-lactamases and therefore have a broader spectrum of activity.

Cephalosporins were classified according to the time of manufacturing and marketing to 4 generations.

3. First-generation cephalosporins

First-generation cephalosporins include cephalexin (Keflex)*, cefadroxil, cefazolin*, cephalothin, cephapirin, and cephradine*. These drugs are very active against gram-positive cocci, such as pneumococci, streptococci, and staphylococci. *E coli, K pneumoniae,* and *Proteus mirabilis* are often sensitive. Cephalosporins are not active against

methicillin-resistant strains of staphylococci (MRSA), *P aeruginosa and Bacteroides fragilis*.

* drugs that are available in our local markets

Pharmacokinetics & Dosage

ORAL

Cephalexin (Keflex), cephradine, and cefadroxil are absorbed from the gut to a variable extent. Urine concentration is usually very high. Cephalexin and cephradine are given orally. Excretion is mainly by glomerular filtration and tubular secretion into the urine. Drugs that block tubular secretion like **probenecid**, may increase serum levels. In patients with impaired renal function, dosage must be reduced.

4. **Second-generation cephalosporins**

Members of the second-generation cephalosporins include **cefaclor, cefamandole, cefonicid, cefuroxime, cefprozil**. In general, they are active against organisms inhibited by first-generation drugs, but in addition they have extended gram-negative coverage.

5. **Third-generation cephalosporins**

Examples: cefotaxime (Claforan)*, ceftazidime*, ceftizoxime*, ceftriaxone*, cefixime (Suprax)*, cefoperazone, cefpodoxime.

*These drugs are available in our local market

Antimicrobial Activity

Compared with first or second-generation agents, these drugs

1. have expanded gram-negative coverage,

2. are able to cross the blood-brain barrier.

3. They are also effective against Beta-lactamase-producing strains of

haemophilus and neisseria.

Ceftazidime and cefoperazone are the only two drugs with useful activity against *P aeruginosa.* Ceftizoxime is active against *B fragilis.*

Cefixime (Trade name: **Suprax**), cefdinir, ceftibuten, are oral agents but:

a. cefixime is much less active against pneumococci (and completely inactive against penicillin-resistant strains)

b. has poor activity against *S aureus.*

Pharmacokinetics & Dosage

Cephalosporins (except oral cephalosporins) penetrate most body fluids and tissues well and, achieve levels in the **cerebrospinal fluid** sufficient to inhibit most pathogens, including gram-negative rods, except pseudomonas.

Examples of pharmacokinetic features of some 3rd generation:

- Ceftriaxone (half-life 7–8 hours) can be injected once every 24 hours. A single daily 1-g dose is sufficient for most serious infections, with 4 g once daily recommended for treatment of meningitis.
- The excretion of ceftriaxone is mainly through the biliary tract, and no dosage adjustment is required in renal insufficiency. The others are excreted by the kidney and therefore require dosage adjustment in renal insufficiency.
- Cefixime (Suprax) can be given orally (200 mg twice daily or 400 mg once daily) for respiratory or urinary tract infections.

Clinical Uses

Third-generation cephalosporins are used to treat a wide variety of serious infections caused by organisms that are resistant to most other drugs. Strains expressing extended-spectrum Beta-lactamases, however, are not susceptible.

a. Meningitis: Ceftriaxone and cefotaxime are approved for treatment meningitis caused by pneumococci, meningococci, *H influenzae,* and susceptible enteric gram-negative rods.

   Ceftriaxone and cefotaxime are the most active cephalosporins against penicillin-resistant strains of pneumococci and are recommended for empirical therapy of serious infections that may be caused by these strains. Meningitis caused by highly penicillin-resistant strains of pneumococci may not respond, and addition of **vancomycin** is recommended.

b. sepsis of unknown cause: This is a potential indication for empirical therapy both in the normal and the immunocompromised patient.

6. Fourth-generation cephalosporins (katzung 2006)

Cefepime is an example of a so-called fourth-generation cephalosporin. It is more resistant to hydrolysis by chromosomal Beta-lactamases (e.g., those produced by enterobacter). It has good activity against:

- *P aeruginosa,*
- *S aureus,* and
- *S pneumoniae*.
- Cefepime is highly active against haemophilus and neisseria.

It penetrates well into cerebrospinal fluid. It is cleared by the kidneys and has a half-life of 2 hours, and its pharmacokinetic properties are very similar to those of ceftazidime. Unlike ceftazidime, however, cefepime has good activity against most penicillin-resistant strains of streptococci,

and it may be useful in treatment of enterobacter infections. Otherwise, its clinical role is similar to that of third-generation cephalosporins.

Adverse effects of cephalosporins

A. Allergy

Cephalosporins are sensitizing and may elicit a variety of hypersensitivity reactions that are identical to those of penicillins, including:

anaphylaxis, fever, skin rashes, granulocytopenia, hemolytic anemia. Nephritis

Local irritation can produce severe pain after intramuscular injection and thrombophlebitis after intravenous injection.

However, the chemical structure of cephalosporins is sufficiently different from that of penicillins so that some individuals who are allergic to penicillin may tolerate cephalosporins. The frequency of cross-allergenicity between the two groups of drugs is uncertain but is probably around 5–10%. However, patients with a history of anaphylaxis to penicillins should not receive cephalosporins.

B. Toxicity

Renal toxicity, including interstitial nephritis and even tubular necrosis.

II. Other inhibitors of cell wall synthesis:

Vancomycin

Vancomycin is an antibiotic produced by *Streptococcus orientalis.* It is active only against gram-positive bacteria, particularly staphylococci.

Antibacterial Activity

Vancomycin is bactericidal for gram-positive bacteria. Most pathogenic staphylococci, including those producing Beta-lactamase and those

resistant to nafcillin and methicillin, are killed. Vancomycin kills staphylococci relatively slowly and only if cells are actively dividing.

Pharmacokinetics

Vancomycin is poorly absorbed from the GIT. It should be given IV and only given orally for the treatment of antibiotic-associated enterocolitis caused by *C difficile*.. The drug is widely distributed in the body such as cerebrospinal fluid (CSF) but to some extent, the distribution to CSF is increased in the presence of meningeal inflammation. 90% of the drug is eliminated by glomerular filtration.

Clinical Uses

The main indications for parenteral vancomycin are:

1. sepsis or endocarditis caused by methicillin-resistant staphylococci (MRSA). However, vancomycin is not as effective as ant staphylococcal penicillin for treatment of serious infections such as endocarditis caused by methicillin-susceptible strains.

2. enterococcal endocarditis: Vancomycin in combination with gentamicin is used in a patient with serious penicillin allergy.

3. meningitis: Vancomycin (in combination with a third generation cephalosporin such as cefotaxime, ceftriaxone, or rifampicin) is also recommended for treatment of suspected or known to be caused by a highly penicillin-resistant strain of pneumococcus.

4. antibiotic-associated enterocolitis: this condition is caused by over growth of *C difficile.* Oral vancomycin, 0.125–0.25 g every 6 hours is used. In case of vancomycin-resistant enterococci, metronidazole can be used

as alternative and vancomycin should be reserved for treatment of refractory cases.

Adverse Reactions

Adverse reactions are encountered in about 10% of cases. Most reactions are minor.

1. phlebitis at the site of injection.

2. Chills and fever

3. Rare ototoxicity and nephrotoxicity, which may be increased with administration of another ototoxic or nephrotoxic drug, such as an aminoglycoside.

4. "red man" or "red neck" syndrome. This is the most common type of reactions, caused by release of histamine.

34. Antibiotics: Part II

The main reference:
Bennett et al (editors). Clinical pharmacology,
Edinburgh …, Churchill Livingstone, Eleventh edition, 2012

The Aminoglycosides

A group similar in chemical structure and properties.

Streptomycin is the first aminoglycoside to be discovered (in 1943 after penicillin). It is also the first anti-mycobacterial drug to be used

Other members

Gentamicin, Kanamycin,

Amikacin (has the widest antibacterial spectrum of aminoglycosides)

Tobramycin (preferred for *Ps. aeruginosa)*,

Netilmicin, Neomycin (Too toxic for systemic use, used topically),

Framycetin (Too toxic for systemic use, used topically)

Mechanism of action

Bactericidal

Interfere with protein synthesis by irreversibly binding to ribosomes (30 S subunits). The incorrect amino acid sequence results in abnormal proteins which are fatal to the microbes

Aminoglycosides exhibit concentration-dependent bacterial killing

That is why the total daily dose can be administered as a single dose instead of the usual twice- or thrice-daily.

Pharmacokinetics

Water soluble (highly polar)

Poor GI absorption

Not given orally (except for bowel sterilization).

Poor passage into the CSF (even if meninges are inflamed).

Eliminated unchanged by the kidney.

Half-life 4 h (in renal impairment increased probably to 100 h causing toxicity).

Plasma concentration should be measured regularly in patients with renal impairment.

Antibacterial activity of aminoglycosides

Bactericidal against aerobic gram –ve organisms (and some gram +ve organisms e.g. staphylococci). Streptomycin and kanamycin are also active against *Mycobacterium tuberculosis*. Tobramycin, gentamicin and amikacin have activity against *Pseudomonas aeruginosa.*

Relatively inactive against anerobes.

Gentamicin

Is active against gram –ve and some gram +ve bacteria

Inactive against anaerobes

Poor activity against streptococci and pneumococci

In undiagnosed serious infections, gentamicin is usually given with a penicillin and/or metronidazole (Why?)

Penicillins (by interfering with cell wall synthesis) greatly enhance the transport of aminoglycosides into the bacterial cell and increase their activity (synergism)

Adverse effects of aminoglycosides

(Mainly Ototoxicity and Nephrotoxicity)

Ototoxicity (8^{th} cranial nerve damage; both auditory and vestibular parts)

Tinnitus is a warning symptom of auditory nerve damage

Motion-related headache, dizziness and nausea are early signs of vestibular toxicity.

Factors predisposing to ototoxicity

Poor renal function

Prolonged duration of treatment

Recent or concurrent treatment with another ototoxic drug (e.g. loop diuretic)

Elderly or debilitating patient

2. Nephrotoxicity

- Dose-related changes in tubular cells
- Risk factors include: Low blood pressure, loop diuretics, advanced age, and the use of another nephrotoxic drug.

3. Neurotoxicity

By competitive neuromuscular block after a large dose; can potentiate neuromuscular blocking drugs.

4. Others: rash, …

Neomycin

Too toxic for parenteral administration

Can be used topically for infection of the skin and mucous membrane

Also used orally to reduce the bacterial population of the colon e.g. before bowel surgery or in hepatic failure (Why?)

Systemic absorption may occur after oral or topical use (toxicity in renal impairment)

Tetracyclines

The first tetracycline was isolated from soil streptomyces microorganisms in 1948

They have a very broad antimicrobial spectrum

Their use decreased because of increased bacterial resistance

Mechanism of action

Bacteriostatic

Reversibly inhibit ribosomal protein synthesis in both bacterial and human cells

Their selectivity to bacteria is due to achieving high intracellular concentration in bacteria because of presence of active transport system (not present in human cells)

Pharmacokinetics

Most tetracyclines are partially absorbed from the GIT (enough remaining to alter the flora)

Can chelate calcium, aluminum and iron (in antacids, iron preparations and dairy products) reducing absorption of both tetracycline and metals (exceptions are doxycycline and minocycline: less chelation)

Excreted mainly unchanged in urine (exceptions: doxycycline and minocycline, mainly non-renal)

Can cross placenta and appear in milk but poor blood brain barrier penetration

Tetracyclines has antianabolic effect (inhibition of protein synthesis in man) resulting in raised blood urea and nitrogen in blood

Tetracycline hydrochloride (the usually used salt) is more soluble than free tetracycline, resulting in acidic solution.

Tetracycline hydrochloride precipitates with increasing gastric pH (e.g. if given with antacids) or in the presence of metallic cations (iron, calcium, aluminum: chelation)

Doxycycline differs from old tetracyclines in that doxycycline has:

- non-renal (hepatic) route of elimination (i.e. can be given in renal impairment)

- better GIT absorption
- Longer half-life (16h); unchanged in renal failure (given once or twice daily)
- less chelation with calcium
- minimal antianabolic effect
- moderate penetration through the CSF (poor with other tetracyclines)

Minocycline has broader spectrum (effective against *Neisseria meningitidis*) but its use is limited because of:

Side effects such as vestibular disturbances (dizziness, vertigo), and greater risk of SLE-like syndrome

Tetracyclines and bones and teeth

Tetracyclines are readily bound to calcium in the newly formed bone and teeth.

During pregnancy or in young children (below 8-12 years), tetracycline can
result in enamel dysplasia with pitting and teeth yellow discoloration and increased susceptibility to caries.

When deposited in bones, it may cause deformity or growth inhibition

Adverse Effects of Tetracyclines

GIT: nausea, vomiting, diarrhea, dysphagia, esophageal irritation

Teeth hypoplasia and bone growth inhibition in children

Prolonged tetracycline therapy can also stain the fingernails at all ages.

Others: hepatoxicity, pancreatitis, blood disorders, …

Clinical Uses

Tetracyclines remain an important choice for treatment of infections caused by:

Chlamydia (trachoma, urethritis, salpingitis,..)

Rickettsia (Q-fever, typhus)

Brucella (doxycline with either streptomycin or rifampicin)

Borrelia (Lyme disease)

Respiratory and genital mycoplasma

Exacerbation of chronic bronchitis

Treatment of acne

Treatment and prophylaxis of malaria

Active against amebae and other protozoa

Demeclocycline is used in treatment of chronic hyponatremia due to inappropriate secretion of ADH. It produces a state of unresponsiveness to ADH.

Tetracycline use should be avoided in:

pregnant or lactating women, in children with developing teeth (permanent dark yellow staining) and may affect the growth of teeth and bones.

Quinolones and Macrolides

Quinolones

Ciprofloxacin, Norfloxacin, Levofloxacin, Others …

[Nalidixic acid, first generation quinolone used in 1962 for UT infection]

Most of the quinolones used now are fluoroquinolones (flourine atom is added to increase antibacterial activity)

Mechanism of action

- Quinolones inhibit bacterial (but not human) DNA gyrase which is responsible for DNA supercoiling . This results in less compact and fragmented DNA.
- They are broad spectrum (G-ve, G+ve, mycoplasma, chlamydia, and some mycobacteria) antimicrobials.
- They are bactericidal with concentration-dependent bacterial killing
- Flouroquinolones can enter inside the cells easily and used to treat intracelluar pathogens e.g. legionella and mycoplasma

Pharmacokinetics

- Well absorbed orally
- Metabolized by the liver with both renal and biliary excretion (no adjustment in renal failure)

Substantial excretion and re-absorption occur through colonic mucosa

- Good penetration to bone and prostatic tissue

Ciprofloxacin

Antibacterial spectrum

Particularly active against gram –ve bacteria (salmonella, shigella, neisseria, pseudomonas, ….)

Moderately active against gram +ve bacteria e.g. *streptococcus pneumoniae*

Also active against chlamydia, mycoplasma and some mycobacteria

Less active against anaerobic organisms

Used in adults to treat:

Respiratory infections (but not pneumococcal pneumonia)

Urinary tract infections

GI infections including typhoid fever

Bone and joint infections (e.g. osteomyelitis from salmonella in sickle cell anemia, good penetration to bone)

GU tract (pyelonephritis, gonorrhea and prostatitis)

Adverse effects

Common side-effects

- Nausea, vomiting, and diarrhea
- Headache, dizziness, confusion
- Risk of crystalluria after excessive alkalinization of urine

Less common side effects

- Tendon problems (rarely tendon rupture, particularly Achellis tendon in elderly and specially when steroids are used)
- Prolongation of QT intervals
- Hemolysis in G6PD deficiency
- Convulsion (particularly if there is history of epilepsy or when used with NSAIDs which potentiate this effect)
- Reversible arthropathy has developed in weight-bearing joints in immature animals after quinolones treatment (Caution in children and adolescents except for serious infections)
- Ciprofloxacin inhibits metabolism of warfarin and theophylline

Dose

250 –750mg twice daily orally

Single oral 500mg dose for gonorrhea (GC)

Can be given intravenously (caution in renal impairment)

Cautions and Contraindications (C/I)

Epilepsy

QT prolongation

CNS lesions (e.g. stroke)

Pregnancy (found, in animal studies, to cause arthropathy)

Generally not indicated in children and adolescents, possibility of musculoskeletal damage: arthropathy occurs in weight-bearing joints in young animals)

Myasthenia gravis (risk of exacerbation)

Patient Education

- Milk, antacids, or medicines containing iron or zinc should not be taken in the 2 hours before or after taking ciprofloxacin (chelation).
- Plenty of water should be taken during the course of ciprofloxacin (to avoid crystalluria).
- Do not take non-steroidal anti-inflammatory drugs (NSAIDs) while you are being treated with ciprofloxacin (risk of convulsion).

Levofloxacin and moxifloxacin

Levofloxacin has greater activity against pneumococci than ciprofloxacin

<u>Macrolide Antibiotics</u>

Are a group of antibiotics which have in common a macrocyclic ring (14 member lactone ring) to which is attached different sugar molecules Erythromycin (isolated in 1952)

Erythromycin derivatives: Clarithromycin and azithromycin (1991)

Mechanism of action

They interfere with protein synthesis by binding to ribosomes of the microorganisms. They do not attach to human ribosomes.

Macrolides are mainly bacteriostatic but can be bactericidal depending on bacterial sensitivity and at high antibiotic concentrations. Its effect is time-dependent

Antibacterial Spectrum of Erythromycin

Erythromycin has similar (but not identical) antibacterial spectrum to penicillin and thus it is an alternative in penicillin-allergic patients. Macrolides are mainly active against gram-positive organisms (cocci and bacilli; mainly staphylococci and streptococci)

Pharmacokinetics of erythromycin

- Oral absorption is incomplete.
- Erythromycin is extensively metabolized.
- It is an enzyme inhibitor; inhibiting oxidation of a number of other drugs.
- Elimination is almost exclusively via the bile and feces
- Half-life (2-4h) is dose-dependent.
- Clarithromycin is metabolized into active metabolites.
- Azithromycin is not metabolized.
- Erythromycin does not penetrate into the CNS.
- It is one of the few antibiotics that diffuse into prostatic tissue.

Uses

- Respiratory tract infection (including *Mycoplasma pneumoniae in children*, diphtheria, whooping cough, Legionella, chlamydia and others)
- GI: Campylobacter enteritis
- Acne
- Alternative in penicillin-allergic patients

Adverse effects

- Mild GI side effects: nausea and diarrhea in 25% of patients (*less frequent with clarithromycin and azithromycin*)
- Less frequently: hepatotoxicity (including cholestatic jaundice particularly with erythromycin estolate)
- Erythromycin and clarithromycin inhibit metabolism of drugs like theophylline, carbamazepine, warfarin, …

Contraindications

- Liver dysfunction

Clarithromycin

- Similar spectrum to erythromycin (i.e. on Gram+) with slightly greater activity against *H. influenza*
- Tissue concentrations are higher (concentrated intracellularly)
- Also used in the regimens for *H. pylori* eradication
- Its metabolite is active
- It is a hepatic enzyme inhibitor
- Given twice daily
- GI side effects are less common.

Azithromycin

- Slightly less activity than erythromycin against Gram-positive bacteria
- Enhanced activity against some important Gram-negative organisms including *H. influenzae.*
- Has a long tissue half-life (50 h), given once daily (plasma concentration is very low, tissue concentration is much higher)
- Remains largely unmetabolized and excreted in bile and feces
- GI side effects (9%) are less than erythromycin

Erythromycin and probably other macrolide antibiotics accelerate gastric emptying into the duodenum. This prokinetic effect is attributed to motilin agonist activity on smooth muscle. Erythromycin, therefore, can be used for treatment of gastroparesis symptoms such as nausea and vomiting and has synergistic activity with metoclopramide and domperidone.

Clindamycin, chloramphenicol, sulfonamides, and others

Clindamycin

- Active against Gram-positive cocci (e.g. penicillin-resistant staphylcocci, and streptococci). It is also effective against many anerobic bacteria especially *Bacteroides fragilis* (e.g. abdominal sepsis)
- Has similar antibacterial spectrum to erythromycin (with which it has a partial cross resistance)
- Well concentrated in bone; Excreted in bile and urine

Clinical Uses

- Staphylococcal bone and joint infections (e.g. osteomyelitis)
- Intra-abdominal sepsis
- Skin and soft tissue infections
- Others (e.g. cellulitis in penicillin-allergic patients, also used in falciparum malaria)

Antibiotic-associated colitis (pseudo-membranous colitis due to *Clostridium difficile*) occurs more frequently with clindamycin; more than any other antibiotics (this colitis is most common in middle-aged and elderly women, especially following operation). Discontinue clindamycin immediately if diarrhea develops

Chlromphenicol (1947)

- A broad spectrum antibiotic
- Associated with serious hematological side effects (Aplastic anemia)
- Should therefore, be reserved for the treatment of life-threatening infections (e.g. those caused by *H. influenzae* and also for typhoid fever)

Chloramphenicol inhibits protein synthesis by inhibiting the enzyme; Peptidyltransferase. It is primarily bacteriostatic (although it is bactericidal to most strains of *H. influenzae* and *Streptococcus pneumonia)*

GIT absorption is very efficient. It is widely distributed, and penetrates into all tissues better than any other antibiotic. Chloramphenicol penetrates well into the eye when used topically or systemically. Eye drops and ear drops are available.

Adverse effects

Rare blood disorders which are of two types:

- **Idiosyncratic, irreversible, non-dose dependent usually fatal aplastic anemia** which might occur during treatment or even weeks after prolonged treatment (may, very rarely, occur even after the use of eye drop).
- **Reversible**, dose-related bone marrow depression.

In neonates, failure of liver to conjugate chloramphenicol and kidney to excrete; high levels result in circulatory collapse (Grey baby syndrome).

Sulfonamides

The first use of sulfonamides for streptococcal infection was in 1936

By their structural resemblance to *p*-aminobenzoic acid (PABA), sulfonamides competitively inhibit PABA cellular uptake and incorporation into folic acid. Therefore, prevent nucleic acid synthesis and bacterial growth and multiplication.

Human cells are not harmed by sulfonamides because human uses preformed folic acid and do not synthesize folic acid.

The use of sulfonamides has decreased because of increasing bacterial resistance and the availability of more active and less toxic antibacterials.

Examples

- **Sulfadiazine** is used for prevention of rheumatic fever recurrence and in treatment of toxoplasmosis.
- **Silver sulfadiazine** is used topically in the prophylaxis and treatment of infections in burn wounds
- **Sulfamethoxazole** is used in combination with trimethoprim as co-trimoxazole. These drugs are used together because of their synergistic activity

  Sulfamethoxazole and trimethoprim inhibit successive steps in the DNA and RNA synthesis. Sulfamethoxazole inhibit biosynthesis of folic acid, and trimethoprim inhibits activation of folic acid (conversion of folic acid [dihydrofolate] to folinic acid [tetrahydrofolate] through inhibition of the enzyme dihydrofolate reductase, DHFR).

This combination (co-trimoxazole) results in:

- Conversion of the two bacteriostatic compounds to bectericidal combination e.g. *proteus* is relatively insensitive to each drug given alone, but can be killed by their combination.

- An increase in the antibacterial spectrum
- Lower doses of each drug are required with less side effects
- Reduction in the emergence of resistant strains

The use of co-trimoxazole is restricted to certain indications because of rare but serious adverse effects e.g. Stevens-Johnson syndrome [severe form of erythema multiforme] and bone marrow depression (agranulocytosis). These may occur especially in the elderly with reports of sudden deaths.

Indications include:

- The drug of choice in *Pneumocystis carinii* pneumonia (a life-threatening infection in immunosuppressed patients)
- Acute exacerbation of chronic bronchitis
- Infections of the urinary tract (if bacteria are sensitive)
- Acute otitis media in children

Adverse effects of sulfonamides other than (erythema multiforme, bone marrow depression) include:

Crystalluria particularly in concentrated and acidic urine.

Hemolysis in G6PD deficiency

Allergic reactions (including fixed drug eruption)

Trimethoprim can be used alone (with good efficacy and less side effects)

for: Urinary tract infection, Respiratory tract infection, Prostatitis, Shigellosis, Invasive salmonella infections (typhoid fever).

<u>Other Antibacterials</u>

Fusidic acid (Sodium fusidate)

Narrow-spectrum antibiotic (Anti-staph)

The only indication for its use is penicillin-resistant staphylococci, especially osteomyelitis (well concentrated in bone). It can also be used for staphylococcal endocarditis

Linezolid

Active against Gram-positive bactreria including methicillin-resistant *staphylococcus aureus* (MRSA)

Polymyxins

(Polymyxin B and Colistin)

- Active against Gram-negative organisms including *pseudomonas aeruginosa and klebsiella pneumoniae*
- Not absorbed by mouth, given intravenously and included in many topical preparations
- Adverse effects: neurotoxicity and nephrotoxicity

Antibacterial drugs indicated only in urinary tract infections.

Example:

Nitrofurantoin

- Effectively concentrated in urine (low plasma level)
- More active in acid urine
- Gastric irritant (nausea and vomiting)
- Active against the majority of urinary tract pathogens except pseudomonas
- Causes hemolysis in G6PD deficiency

Imidazoles

Metronidazole

Antibacterial (anaerobic bacteria e.g. Bacteroides and Clostridia) and antiprotozoal.

Mechanism: It is converted to active form by reduction of its nitrogroup to bind to DNA and prevents its replication. This reduction occurs only in anaerobic bacteria).

Used for treatment or prevention of sepsis in which anaerobic bacteria contribute e.g. GIT and gynecological surgery, acute ulcerative gingivitis.

And for protozoal infections

Side effects: GI (nausea, vomiting, metallic taste, ..), CNS (headache, dizziness, peripheral neuropathy, seizures, ..)

Tinidazole: Similar to metronidazole but has longer half-life, can be given once daily

35. Antifungal Drugs

Classification:

1-Drugs that disrupt the fungal cell membrane:

a-Polyene antibiotics (polyene =possesses ring structure with several conjugated bonds) e.x. amphotericin B; nystatin

b- Azoles ex. Fluconazole; ketoconazole; itraconazole

c-Allylamines e.x. terbinafine

2-Drugs that inhibit mitosis e.x. griseofulvin

3-Drugs that inhibit DNA synthesis e.x. flucytosine

Polyene antibiotics

Mechanism of action: binds with ergosterol, an essential component of fungal cell membrane, increasing its permeability leading to leakage of ions and enzymes which results in cell death**.**

Amphotericin B:

is not absorbed orally, administered by i.v. infusion for systemic fungal infections.

half-life is 15 days because it binds to cholesterol in human cell membranes and to lipoproteins.

other Uses: Leishmaniasis

Side-effects: 1) acute infusion reactions as fever, chills, hypotension, vomiting and dyspnea 2) nephrotoxicity 3) hypokalaemia and hypomagnesaemia 4) muscle and joint pain. 5) normocytic normochromic anaemia due to bone marrow suppression 6) weight loss

Nystatin:

is too toxic for systemic use.

is not absorbed from GIT and is used orally as tablets or solution to treat or prevent superficial candidiasis of the mouth, eosophageous or intestinal tract.

It is used topically (cream, ointment) for candidiasis of skin or suppositories for vagina.

AZOLES

Mechanism of action: inhibits synthesis of fungal ergosterol. This causes cell membrane to become permeable and leakage of intracellular constituents resulting in fungal cell death.

Ketoconazole:

PKs: Oral absorption requires an acidic PH.

- It is widely distributed in tissues; effective in systemic fungal infections but Lack *of selectivity in action* results in an important side effects so its use is superseded by fluconazole and itraconazole.
- Poorly penetrates into CSF, not effective in fungal meningitis**.**
- can be used topically for cutaneous fungal **infections**.
- It is metabolized in liver and excreted in bile, dose need to be reduced in liver impairment.

Side effects:

1- impairment of human's sterols (androgen and estradiol) synthesis can cause gynaecomastia, decreased libido and menstrual irregularities.
2- hepatotoxicity with elevated liver enzymes, jaundice and fatal hepatic necrosis 3- teratogenic

Interactions:

1) Drugs that lower gastric acidity as antacids, H2 receptor blockers and proton pump inhibitors decrease its absorption.

2) Disulfiram –like reaction with alcohol.

3) Enzyme inhibitor: inhibits metabolism can precipitate toxicity of warfarin, phenytoin, cyclosporin (or cyclosporine) and ventricular arrhythmias with terfenadine

Uses other than antifungal:

1) Androgen-dependent prostate cancer because it suppresses androgen synthesis.
2) Cushing's syndrome because it can inhibit glucocorticoids synthesis.

Fluconazole:

PKs: oral absorption is not affected by the stomach PH.

- It is effective orally for treatment and prevention of oral, esophageal, vaginal, nail and for systemic fungal infections (by Intravenous route).
- has good CSF penetration; effective in fungal meningitis.
- It is excreted unchanged in urine so dose must be reduced in renal impairment.
- t1/2 is long (30 hours), allowing once-a-day administration.
- doesn't inhibit human's sterols synthesis, no endocrine side effects.
- It is teratogenic.

ALLYLAMINES

Terbinafine

Mechanism: fungicidal, interfere with ergosterol synthesis and thereby the formation of the fungal cell membrane.

is highly lipophilic, keratinophilic, concentrated in fatty tissues, skin and nail beds.

Uses: topically for dermatophyte infections of the skin and orally for infections of nails and hair.

Efficacy is more, treatment course is shorter and relapse rate is lower than griseofulvin.

side effects: nausea, diarrhea dyspepsia, rashes, headache (when given orally).

OTHERS

flucytosine

Mechanism: it is metabolized in the fungal cell to 5-flurouracil which inhibits fungal DNA synthesis.

- Excreted unchanged in urine (dose must be reduced in renal impairment).
- has narrow antifungal spectrum and resistance develops rapidly, if used alone. Usually given in combination with amphotericin B, which increases permeability of the fungal cell membrane so increases penetration of flucytosine into it.

Side effects: 1) Nausea, vomiting and bone marrow suppression

griseofulvin

Mechanism: It binds to the newly synthesized keratin in cells of the hair follicles, skin and nail beds (for dermatophytes specifically infect keratinous tissues) it is fungi static: inhibits fungal growth by inhibiting mitosis. It does not affect fungus in the already infected keratin, but it prevents infection of the new keratin, so treatment must be prolonged for several months until infected keratin is shaded off, to avoid relapse.

- is ineffective topically, **given orally,** fatty food enhance absorption .
- USE: superficial dermatophyte infection of skin, hair, and nails.

- ❖ Side effects: 1)- enzyme inducer may reduce effect of several drugs as warfarin and induces disulfiram –reaction with alcohol
  2)headache, CNS disturbances 3) allergic rash 4)GIT upset
  5- photosensitivity

Tolnaftate: topical agent for dermatophytes of skin.

Drugs for superficial (skin, mucous membranes, hair, nail) fungal infections: terbinafine, griseofulvin , tolnaftate, fluconazole, ketoconazole, clotrimazole, amphotericin B and nystatin

- ➢ *NOTE: Fungal **nail infection**:* **requires oral** treatment, **topical** therapy is **not effective**.
  Drugs: fluconazole, ketoconazole, terbinafine, griseofulvin

- ❖ **Drugs for deep fungal infections**: amphotericin B, flucytosine, fluconazole, ketoconazole

36. Antiviral Drugs

Viral infections are difficult to treat for the following reasons:

1. Viruses live inside the host cells (intracellular)

2. The viral replication depends on the synthetic processes of the host cell

3. No standard in vitro susceptibility test

4. The antiviral agent to be effective must either block viral entry or exit from the cell or it is active inside the cell

5. The non-selective inhibitors of viral replication may interfere with host cell function and produce toxicity.

6. Replication of virus usually maximum before the manifestation of clinical symptoms

Stages of viral infection:

1. Adsorption and penetration into susceptible cell

2. Uncoating of viral nucleic acid

3. Synthesis of early regulatory proteins as nucleic acid polymerase

4. Synthesis of RNA or DNA

5. Synthesis of late structural proteins

6. Assembly (maturation) of viral particles

7. Release from the cell

Antiviral drugs can affect (target) any of these steps

Anti-herpes agents:

Aciclovir (acyclovir):

Mechanism of action: acyclovir is a synthetic guanosine derivative, its activated inside the viral infected cell by phosphorylation by the action of the enzyme thymidine kinase (viral enzyme) and then further phosphorylated by the host cell. The phosphorylated acyclovir inhibits viral DNA synthesis

Resistance to the action of acyclovir can develop by enzymes alteration in thymidine kinase or DNA polymerase.

Pharmacokinetics: Available as oral, intravenous and topical formulations. Oral bioavailability is about 20%.Exreted mainly by glomerular filtration and tubular secretion

Penetrates well into various body tissues including the CNS

Clinical uses:

a. primary and recurrent genital herpes (HSV2) usually given orally

b. herpes simplex encephalitis (HSV-1) by IV administration

c. Varicella- zoster usually at higher doses may reduce duration of pain and disease complications

d. herpes keratitis (topical as eye drops)

Adverse effects: 1. well tolerated

2. nausea diarrhea and headache

3. I.V. infusion may cause renal insufficiency and CNS toxicity

Other related drugs:

Idoxuridine……used for herpes simplex infections

Famciclovir…… useful genital herpes and acute herpes

Ganciclovir……..guanosine analogue active against CMV (cytomegalovirus virus), HSV, and VZV

Fascine and cidovir …… do not require activation by thymidine kinase, so may be active against acyclovir resistant viruses.

Antiretroviral Agents:

Nucleoside reverse transcriptase inhibitors:

Zidovudine:

Mechanism of action: zidovudine is a thymidine analogue; it acts by inhibition of reverse transcriptase (leads to inhibition of DNA synthesis from RNA) by incorporation into growing viral DNA chain and cause termination of synthesis.

Kinetics: well absorbed from the GIT and distributed into body tissues including the CSF it is eliminated primarily by renal excretion and clearance reduce in renal impairment

Clinical uses: useful in HIV infection it decreases the rate of clinical disease progression and prolonged survival in HIV infected individuals. Resistance might occur.

Adverse effects: GI disturbances, headache, dizziness and myelosupression with anemia and neutropenia.

Adverse effects: GIT disturbances, myelosupression, neutropenia and headache and insomnia.

Other agents:

Didanosine Lamivudine Zalcitabine Stavudine

Protease Inhibitors:

INDINAVIR, RITONAVIR, SAQUINAVIR NELFINAVIR

Acts by inhibiting protease enzymes which are responsible for the synthesis of proteins for the virion core (by breaking down of the polyproteins)

Anti-influenza agents:

Amantadine and Rimatadine:

Acts by inhibiting uncoating of viral RNA of influenza A within infected host cell thus preventing its replication. Useful in preventing viral infections in high-risk individuals. Both drugs reduce the duration of symptoms of influenza when given early.

Adverse effects: gastrointestinal intolerance CNS symptoms include nervousness difficulty in concentration and headache

ZANAMIVIR, OSELTAMIVIR

Both acts by inhibiting neuraminidase enzyme, which is essential for viral replication and release. Both approved for the treatment of acute uncomplicated influenza infection.

Zanamavir is given by intranasal route; it has poor oral bioavailability low protein binding and rapid renal excretion

Oseltamivir is a pro-drug which is given orally and activated in the gut and liver.

Both drugs can alleviate the symptoms of influenza early especially when given within 30 hours after the onset of symptoms

Interferons:

Endogenous are group of endogenous protein substances produce by the viral infected cells. There are different types of interferons as α, β, γ (alpha, beta and gamma). Interferons-α are the principal interferons synthesized by the white blood cells

Mechanism of action of interferons –α:

1. Inhibiting viral multiplication by inhibiting viral mRNA translation
2. stimulation of macrophage activity
3. induce the formation of interleukins

Interferons can be synthesized by recombinant DNA technology and are especially useful in the treatment of viral hepatitis

Drugs used in viral hepatitis:

Acute hepatitis C ⟶ interferon –α

Chronic hepatitis B ⟶ Interferon-α

Peginterferon – α 2a

Lamivudine (reverse transcriptase inhibitor) useful in Initial phase of the disease

Chronic hepatitis C ⟶ Peginterferon-α 2a

Ribavirin

Peginterferon-α 2a:

It is an interferon which is conjugated with polyethylene glycol (pegylated). This conjugation prolong the duration of action of interferons

Principle classes of antiviral drugs(Rang and Dale's)

Type	Examples	Therapeutic uses
Nucleotide reverse transcriptase inhibitors	Zidovudine Lamivudine Didanosine Abacavir	Mainly HIV in combination with other drugs Lamivudine in hepatitis B
Non-nucleotide reverse transcriptase inhibitors	Efavirenz nevirapine	HIV in combination with other antiviral drugs
Protease inhibitors	Indinavir ritonavir	HIV in combination
Viral DNA polymerase inhibitors	Aciclovir Cidofovir Ganciclovir Foscarnet valaciclovir	Herpes , cytomegalovirus, hepatitis C and respiratory syncitial virus infection
Inhibitors of viral uncoating and neuraminidase inhibitors	Amantadine Oseltemivir	Influenza A, B
Biologicals	Interferon-α Peginterferon-α	Hepatitis B and C and respiratory syncitial virus

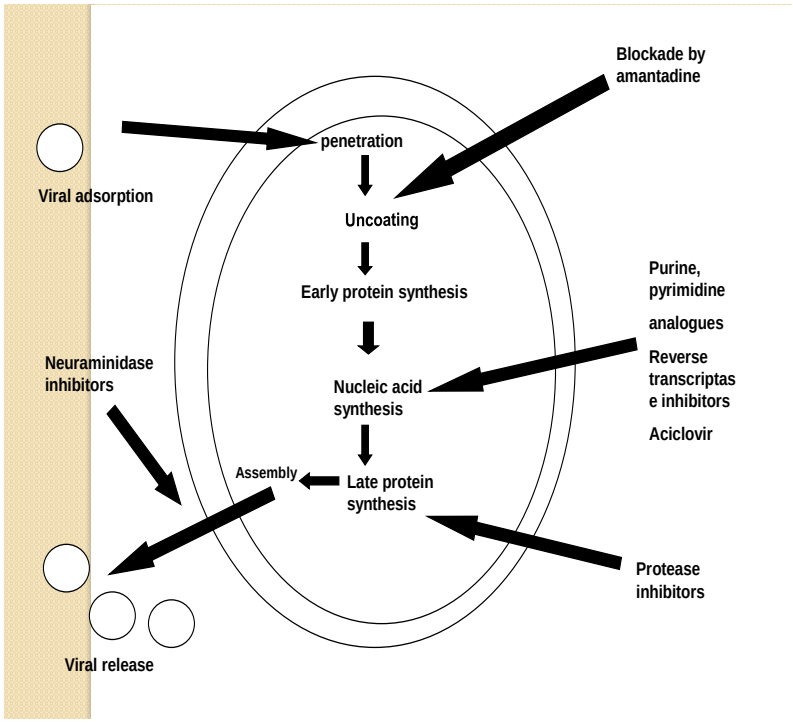


Figure 1 : Illustration of antiviral drugs site of action

37 (1). Anthelmintic Drugs

Drugs for some common parasitic worms

	Enterobius vermicularis **(Pin worms)**	***Ascaris lumbricoids***	***Ankylstoma dudenale***	***E. granulosus*** **(hydatid cyst)**	**Neuro-cysticercosis** (due to the larval form of *Taenia solium*):
Mebendazole	100 mg once; repeated in 2 weeks to kill any worm that may have hatched from eggs after initial treatment	1oo mg twelve hourly For 3 days	100 mg twelve hourly For 3 days		
Albendazole	400 mg once; repeated in 2 weeks	400 mg once	400 mg once	15mg/kg for 3 months	15mg/Kg for one month
Piperazine	75 mg/Kg (max. 3.5 gm) once a day for 7 days	4 gm once a day for 2 days			
Pyrantel pamoate	10 mg /Kg once repeated in 2 weeks	10 mg/Kg once	10 mg/Kg once		
Levamisole		150 mg single dose	150 mg 2 doses at 12 hour interval		

For pin worms (Enterobius vermicularis)

- Personal hygiene : washing hands before eating and after toilet, scrubbing nails, changing underwear, and washing anal region on awakening to remove worm eggs is important to break the cycle of autoinfection.
- All family members should be treated at the same time regardless of whether or not symptoms are present to avoid transmission the parasite.

Ankylstoma duodenal infestation may cause anaemia which require iron supplement.

MEBENDAZOLE

Mechanism of action: prevents uptake of glucose by susceptible intestinal worms, this results in energy depletion, immobilization followed by slow death . It is useful for *pin worms , Ankylstoma, and Ascaris* .

PKs: Tablet should be chewed before swallowing, Food particularly fatty foods increase absorption, so better to be administered on empty stomach .Only 10% of oral dose is absorbed, and rapidly metabolized , so side effects are low including : abdominal pain, diarrhea and hypersensitivity.

It is contraindicated in children below 2 years (not well studied in this age group) and during pregnancy because it is embryotoxic and teratogenic in animals.

ALBENDAZOLE

Mechanism of action is similar to mebendazole. It is effective against intestinal pin worms, *Ascaris* , *Ankylstoma* , eggs of *Ascaris lumbrecoids*.

After absorption it is converted to active metabolites which is distributed to body tissues and act against tissue parasites as hydatid cyst *(* due to larva of *Echinococcus granulosus* or neurocystisercosis (due to larva of *T. solium*) .

It is poorly absorbed orally. Absorption is enhanced by fatty meals, so it is given on empty stomach for intestinal parasites and with fatty meals for tissue parasites

Side effects: high doses and prolonged use cause hepatotoxicity, leukopaenia (Liver function test and blood counts should be done periodically).

Contraindication: pregnancy (teratogenic) and children below 2 years.

PIPERAZINE citrate

It blocks nicotinic receptors at worm's neuromuscular junction resulting in flaccid paralysis f then worm is evacuated in the faeces.

Its use is declined due to its neurotoxic side effects. It may exacerbate seizures in epileptic , so it is Contraindicated in patient with epilepsy.

LEVAMISOLE: alternative to mebendazole and albendazole for intestinal *worms, ankylstoma and Ascaris*.

is a depolarizing neuromuscular blocker that cause depolarization followed by paralysis of and expulsion of live worms in faeces.

Contraindications: pregnancy and children below 2 years.

Drugs for schistomiasis

PRAZIQUANTIL:.

Mechanism: causes spastic paralysis of adult worms and larvae resulting in detachment of worms from tissues and worm's death.

USES:

1- tape worms (T. solium, T. saginata), H. nana 2- neurocystisercosis

3- schistomiasis : It is used in mass treatment control programs for schistomiasis because it is effective against all species of schistomiasis(useful in mixed infections), cures in a single dose, is well tolerated and this will improve compliance

Side effects: nausea, headache, drowsiness

Contraindications: Pregnancy, breast feeding , ocular cysticercosis

METRIFONATE:

Is a cholinesterase inhibitor; causes paralysis of the worm.

It cures only S. haematobium infection with single dose or divided doses in one day. It can be used as monthly prophylactic in endemic areas.

Side effects: headache, vertigo, abdominal pain, diarrhea, vomiting

Drugs for taeniasis

PRAZIQUANTIL

NICLOSAMIDE

Blocks glucose uptake in intestinal tape worms resulting in energy depletion, immobilization and finally death. It is lethal to scolex and segments but not for ova. Purgative is given after niclosamide administration to evacuate the dead segments and prevent occurrence of cysticercosis that results from digestion of larval forms and liberation of ova.

The tablet should be chewed before swallowing and taken on empty stomach.

Uses: T. solium, T. saginata, H. nana

Side effects: mild GIT disturbance

Drugs for filariasis

DIETHYLCARBAMAZINE

Kills both microfilaria and adult parasite. Initial dose is best kept low because deaths of numerous parasite produce immediate reactions as vomiting, headache, urticaria, fever and asthmatic attack due to release of antigenic particles.

Ivermectin: is effective in single dose. It may cause immediate reactions (similar to diethylcarbamazine) due to death of the parasite.

37 (2). Antiprotozoal Drugs

Drugs for amoebiasis

Tissue amoebicides:

a) **For both intestinal and extra intestinal amoebiasis**:

-Metronidazole and tinidazole

- Emetine and dehydroemetine (use is declined because of cardiac toxicity)

b) **For extra intestinal amoebiasis :** chloroquine

Metronidazole

Spectrum of activity*:*

1-protozoa: *E. histolytica, giardia lamblia, trichomonas vaginalis*

2-anaerobic bacteria: *Cl difficile, Cl perfringes, H.pylori, fusobacterium, bacteroides fragilis and gardenerella vaginalis*

Mechanism of action: inside the anaerobic bacteria and sensitive protozoa . metronidazole is converted into an active form by reduction of its nitro group; this binds to DNA and prevents nucleic acid synthesis; it is bacteriostatic.

It is effective against trophozoites but not the cysts of *E.histolytica* .

Kinetics: It is well absorbed after oral or rectal administration.

achieves sufficient concentration to eradicate infection in intestinal wall, pelvic tissues, liver, brain, CSF, semen and vaginal fluid and it can cross the placenta

is metabolized in liver and is excreted in urine, inducing a harmless dark - brown color. Plasma $t_{1/2}$ is 8 hrs.; administered 8 hourly.

Uses*:*

1) amoebiasis including acute intestinal amoebic dysentery, amoebic hepatitis and amoebic liver abscess.

2) giardiasis 3) urogenital trichomoniasis in both sexes

4) anaerobic bacterial infections as: postsurgical infections, intra-abdominal infections , septicaemia , oesteomylitis, brain and lung abscess

5) anaerobic vaginosis 6) pseudomembraneous colitis (caused by *Cl. Difficille*), due to use of some antibiotics.

7) acute ulcerative gingivitis and dental infections

8) eradication of H. pylori associated with peptic ulcer

9)cutaneous leshmaniasis

Side effects

1-GIT: nausea, vomiting, metallic taste, furred tongue

2- CNS: headache, dizziness, vertigo, ataxia, peripheral neuropathy, high doses may cause seizures

3- Disulfiram-like effect with alcohol(nausea , vomiting, sweating, flushing, tachycardia, hypotension).

4- carcinogenic in rodents and mutagenic in bacteria so it is not recommended during 1st trimester of pregnancy and cautiously used later on.

5-Inhibits metabolism and Potentiates anticoagulant effect of warfarin.

Tinidazole

Similar to metronidazole in efficacy and spectrum of activity but:

- It has longer duration of action, allowing once daily administration. single (2g) dose is effective for giardiasis, trichomoniasis and acute ulcerative gingivitis.
- lower side effects

Chloroquine

is an antimalarial drug; highly concentrated in liver ; used for prevention and treatment of amebic liver abscess.

2. **Lumenal amoebicides**

-act in intestinal lumen but do not have tissue amoebicidal action

- must be administered with or after tissue amoebicides during treatment of acute intestinal dysentery or liver abscess, **to eradicate cysts (the infective stage of the parasite)** from the colon and prevent carriers.

- Cure the asymptomatic cyst passers.

a. Diloxanide furoate

Mechanism of action: Oral dose is hydrolyzed by intestinal flora into diloxanide and furoic acid; about 90% of the diloxanide is absorbed, metabolized in liver and excreted in the urine. The unabsorbed fraction reaches colon and acts as a luminal amoebicide; kills trophozoites responsible for production of cysts and eradicates cysts in the lumen of the colon.

adverse effects: flatulence, nausea, abdominal pain, proteinuria and rashes.

b) Iodoquinol is an iodinated hydroxyquinolone. Kills the cyst-forming trophozoites

Other uses: Trichomoniasis, giardiasis

Side effects: Thyroid enlargement, optic atrophy, visual loss, skin rash, anorexia, diarrhea, abdominal pain.

c)Antibiotics: Paromomycin, Tetracycline, Doxycycline

Paromomycin :

is an aminoglycoside antibiotic, given orally, doesn't absorbed, reaches colon in large amounts. It has a direct action on the cyst membrane causing leakage of intracellular components and indirect action as it inhibits colonic flora on which the amoeba feed so reduces proliferation of the amoeba in intestinal lumen.

Other Uses:

- Cutaneous and visceral Leishmaniasis

Adverse Effects: abdominal cramps, nausea and vomiting

Tetracycline & Doxycycline

Mechanism:

They eradicate colonic flora on which amoeba feed so reduce proliferation of the amoeba in intestinal lumen which reduces the risk of intestinal invasion, perforation and peritonitis.

Drugs for TOXOPLASMOSIS

1)Spiramycin (macrolide antibiotic) for toxoplasmosis in pregnant women.

2) Combination of pyrimethamine with sulphadiazine, clindamycin, clarithromycin or azithromycin.

DRUGS FOR LEISHMANIASIS

Sod.stibogluconate:

is poorly absorbed orally; administered IV, IM or intralesionally

has a cumulative effect on repeated administration because it remains stored in tissues.

Side effects: pain and stiffness at injection site, bradycardia and ECG changes.

Pentamidine: administered i.m. or i.v

Mechanism: unknown.

Side effects: hypotension, fainting and dyspnea, due to histamine release

OTHERS: amphotercin B, metronidazole, paromomycin

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38. Antituberculosis Drugs

A) 1st line drugs: Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin are efficacious and have acceptable degree of toxicity.

Principles of antituberculosis therapy:

- Treat persisters (semidormant combination therapy, at least three drugs must be used to:

-Kill large number of rapidly multiplying bacilli; INH is bactericidal against replicating bacteria

-intracellular bacilli that metabolize slowly or intermittently and can cause relapse) Rifampicin and Pyrazinamide are most efficacious.

-Prevent the emergence of drug resistant mutants: rifampicin, INH and ethambutol achieve this.

-INH, rifampicin, ethambutol and pyrazinamide are given orally .

Isoniazid (isonicotinic acid hydrazide) (INH)

Mechanism of action: It is selectively effective to mycobacterium tuberculosis because it prevents synthesis of mycolic acids (a component that is unique to mycobacterial cell walls). It is effective against both intracellular (within macrophages) and extracellular bacilli.

PKs: It is well absorbed from the GIT. Food and aluminum –containing antacids reduce absorption. It is distributed into all body tissues, tubercular cavities, CSF and meninges, hence it is also effective for treatment of tuberculous meningitis.

It is metabolized in liver by acetylation and the rate of the reaction is genetically bimodally distributed. The persons are either ‘‘slow’’ or ‘‘fast’’ acetylators .

Acetylation status does not affect response to drug when INH is taken daily but biweekly regimens are less effective in fast acetylators and peripheral neuropathy-side effect is more common in slow acetylators.

Side effects:

1-Peripheral neuropathy: paresthesia and numbness of the finger tips; due to pyridoxine (vitamin B6) deficiency, because INH is a structural analog of pyridoxine and increases its renal excretion. Neuropathy is more common in slow acetylators, malnourished, elderly, liver diseases and alcoholics. Pyridoxine supplement prevents neuropathy without interfering with the therapeutic effect of INH.

2-liver damage (due to its metabolite acetylhydrazine) range from loss of appetite, nausea, vomiting, jaundice, right upper quadrant pain, elevation of liver enzymes to fatal hepatitis.

- ❖ Liver function tests should be monitored monthly.

3- mental disturbance, optic neuritis and convulsions.

4- INH inhibits metabolism of phenytoin carbamazepin and ethosuximide, increasing their blood level and toxicity.

2-Rifampicin (Rifampin):

Mechanism of action: inhibits bacterial RNA synthesis. It is particularly effective against semidormant intracellular mycobacteria.

It also has activity against M. *leopori*, Staphylococcus*, Niesseria meningitides, Influenza and Legionella* species.

Pharmacokinetics: It is well absorbed orally, distributed widely in body fluids and tissues. Since the substance itself is red, its distribution is the reason for the orange-red color of the saliva, tears and sweat. It is excreted in urine and faeces. The red color of urine can be used as a

marker for whether or not the drug has been effectively absorbed and to detect non-compliance.

It penetrates well into CSF when meninges are inflamed. The half-life is shortened on repeated dosing because, as an enzyme inducer it increases its own metabolism.

Uses:

1-treatment of tuberculosis 2- serious Staphylococcus *aureus* infections such as osteomyelitis and endocarditis 3-brucellosis 4-leprosy 5-elimination of nasal carriers of meningococci, because it can distribute to nasal secretions.

6-prophylaxis in contacts of patients with *Haemophilus influenza* type b.

Side effects: 1- hepatitis, jaundice 2-thrombocytopenia 3- pruritus and rash 4- if administered less often than twice weekly it causes immunological reactions characterized by Flu-like symptoms (chills, fever, and muscle pain), acute haemolytic anemia, thrombocytopenia and acute renal failure

5 –harmless red discoloration of urine, sweat and tears

6-It induces Cytochrome P450 enzymes which increases the elimination of many other drugs as warfarin , oral contraceptives, sulfonylureas, and phenytoin; dose of these drugs need to be increased to avoid treatment failure.

3-Pyrazinamide:

- is a derivative of nicotinamide.

- is included in combination therapy of tuberculosis because it can kill persisters (dormant) intracellular mycobacteria that may cause relapse. It is taken by macrophages and diffuses into mycobacteria where it is

converted to pyrazinoic acid- the active form of the drug- by mycobacterial pyrazinamidase.

-Pyrazinamide is only used in the first two months of treatment as it losses effectiveness after that because the enzyme pyrazinamidase is only effective at acidic PH which is available inside phagolysosomes in macrophages, that present in huge amount during the early stages of the disease.

-It can cross into CSF so it is also useful in tuberculous meningitis.

Side effects: hyperuricemia and joint pain, hepatitis, jaundice, urticaria

4-Ethambutol:

-is a bacteriostatic, usually given in combination therapy with other antituberculosis drugs to delay or prevent the emergence of resistant bacilli.

-can cross the inflamed meninges and is useful in tuberculous meningitis.

-is excreted unchanged by the kidneys, the dose should be reduced in renal impairment.

Side effects: Optic neuritis resulting in loss of visual acuity and red-green color blindness hence it is contraindicated in children aged 6 years and below as they are too young to notice deterioration in their visual acuity so may end with blindness.

Periodic test of vision must be done throughout the treatment period.

5- Streptomycin an aminoglycoside, administered by IM injection.

Treatment regimen of tuberculosis:

1. **Unsupervised regimen**: drugs are taken by the patient himself daily. The drugs are INH and rifampicin for 6 months, plus pyrazinamide for the first 2 months.

2. DOTs (directly observed treatment short course). Drugs are given under supervision of a health provider to improve compliance: Thrice weekly INH and rifampicin for 6 months, plus pyrazinamide for the first 2 months.

- ❖ With both regimen , ethambutol or streptomycin must be added if there is a possibility of drug resistant organism or if the patient is severely ill with extensive active lesions
- ❖ The initial 2 months three drugs treatment phase aim to reduce number of bacilli as rapidly as possible and render the sputum non-infectious. The use of rifampicin and INH for 4 additional months aims to eliminate the remaining intracellular bacteria and prevent relapse.

Chemoprophylaxis for tuberculosis

For symptom- free persons in contact with disease, who develop a positive tuberculin test.

- ❖ INH twice weekly for 9 months
- ❖ Rifampicin daily for 4 months

B)2nd line drugs: are either less effective or more toxic than the first line drugs and they are used when there is intolerance or resistance to 1st line drugs.

Ex.kanamycin, amikacin, ethionamide, Ciprofloxacin, levofloxacin clarithromycin, rifabutin, capreomycin and rifapentine

39. Malaria and antimalarial drugs

Overview:

- 500 million having the disease each year with more than 90% of these occurring in Africa.
- Malaria causes up to 2.7 million deaths per year with the vast majority of these among young children in Africa.
- Malaria is presented as high fever, shivering, pain in the joints, headache, repeated vomiting, generalized convulsions and coma. Symptoms only become apparent 7-9 days after being bitten by an infected mosquito.

Life cycle of the malaria parasite

The life cycle consists of:

1. A *sexual cycle*, which takes place in the female *anopheles mosquito*, and an *asexual cycle*, which occurs in humans (figure 1).

   Female mosquito bites human ⟶ inject little number of ***sporozoites*** ⟶ into the bloodstream. Within 30 minutes ⟶ enter the liver. where, during the next 10-14 days, they undergo a ***pre-erythrocytic stage*** resulting in development of ***merozoites*** which enter the red cells and form motile intracellular parasites termed ***trophozoites***. This stage is called erythrocytic *stage*.

   Inside the RBC, the parasite digests the haemoglobin and used it as a source of amino acid. Free haem which results from digestion of haemoglobin is toxic to the parasite but it

is changed by the parasite to harmless compound by polymerisation to ***hemozoin***. Some antimalarial drugs act by inhibiting the haem polymerase (see below). ***Schizont*** is a phase of parasite at rapid growth and multiplication. This results in the production of further **merozoites**, which are released when the red cell ruptures. These merozoites then bind to and enter fresh red cells and the erythrocytic cycle starts all over again. In certain forms of malaria, some sporozoites on entering the liver cells form ***hypnozoites***, or 'sleeping' forms of the parasite, which last in the liver for many months or years and can results in relapse after this period of time.

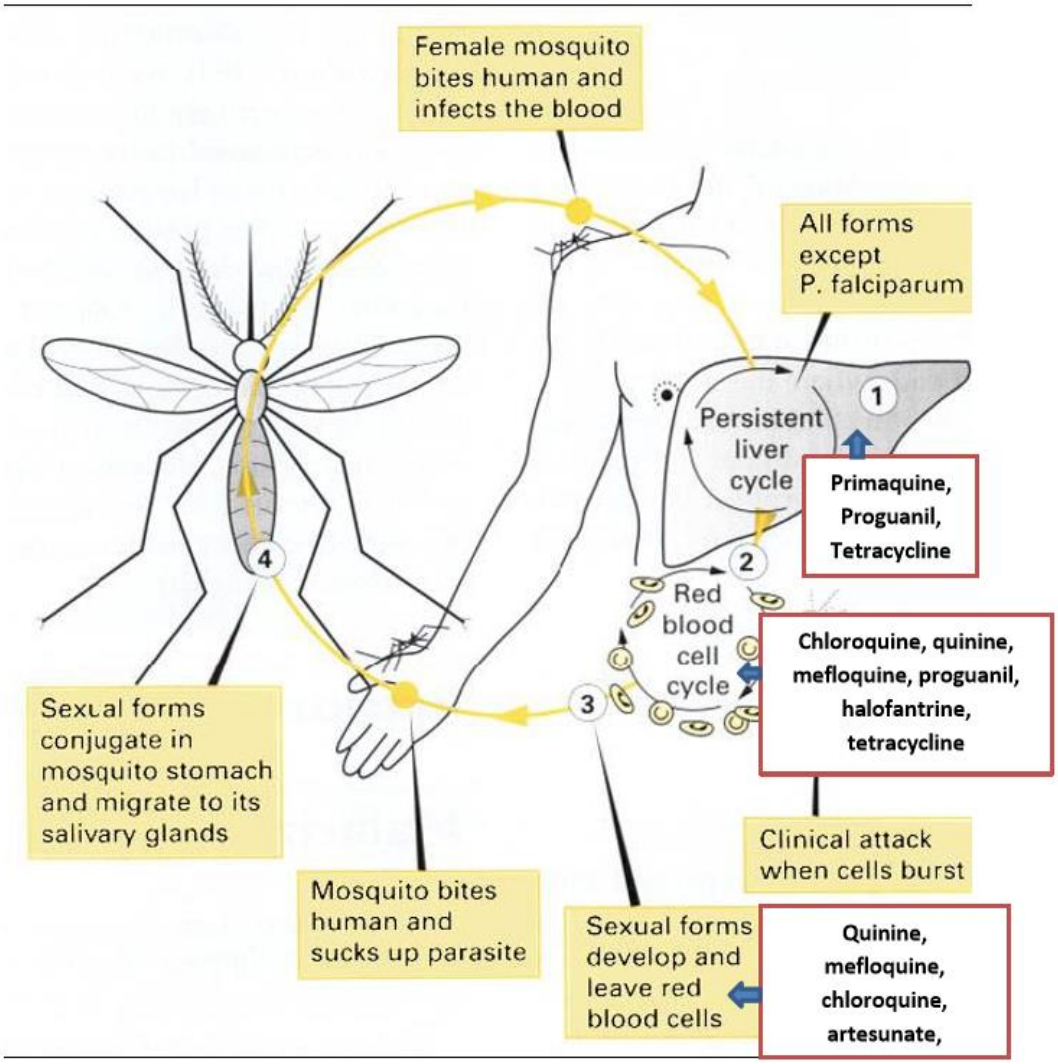


Figure 1: life cycle of malaria parasite and names of drugs used at various stages (modified from Bennett, Brown, Sharma, 2012).

Clinical feature of malaria is manifested as cyclic episodes of fever which result from the synchronized rupture of red cells with release of parasites and toxins.

Relapses of malaria are likely to occur with those forms of malaria that have **exoerythrocytic cycles (liver cycle)**.

Human Malaria parasite is present in four species:

1. ***P. falciparum***
    a. has an erythrocytic cycle of 48 hours in humans
    b. produces *malignant tertian malaria*-'tertian' because the fever was believed to recur every third day, 'malignant' because it is the most severe form of malaria and can be fatal.
    c. The *P. falciparum* makes changes in red blood cells (RBC) leading to adhesion of (RBC) to vascular endothelial cells, or to other uninfected red cells forming clumps (rosettes) and finally occluding and interfering with microcirculation and tissue perfusion causing organ dysfunction, for example renal failure and encephalopathy (cerebral malaria).
    d. *P. falciparum* does not have an exoerythrocytic stage (liver stage), so by eradicating the erythrocytic stage, relapses do not occur.
2. ***P. vivax***

a. produces benign tertian malaria-'benign' because it is less severe than falciparum malaria and rarely fatal.
b. Exoerythrocytic forms (liver stage) may persist for years and cause relapses

3. ***P. ovale***: has a 48-hour cycle.
4. ***P. malariae***: has a 72-hour cycle, causes *quartan malaria* and has no exoerythrocytic cycle.

Antimalarial drugs

The best way to treat malaria is to avoid the disease in the first place by preventing mosquito bites. Travellers to infected areas should cover their skin and using insect repellents. Bed nets sprayed with insecticides such as permethrin can also be very effective.

classification of antimalarial drugs

A. Blood Schizontocides:

These drugs kill the parasite in the blood.

- Resulting in a cure of infections with *P. falciparum* or *P. malariae*, which have no **exoerythrocytic stage (liver stage)**
- with *P. vivax* or *P. ovale*, the drugs suppress the actual attack but exoerythrocytic forms can cause later relapses.

List of Blood Schizontocides drugs:

1. chloroquine	2. quinine	3. mefloquine
4. halofantrine	5. proguanil	6. pyremethamine
7. tetracyclines		

B. Tissue Schizontocides:

These drugs kill the parasite at the liver stage and so called **tissue schizontocides** and are used for radical cure of malaria. These drugs are not required for *P. falciparum* or *P. malariae*, which have no **exoerythrocytic stage**.

List of Tissue Schizontocides drugs:

1. primaquine	2. proguanil	3. tetracyclines

C. Gametocytocides:

These drugs act on the sexual forms in the red blood cells, the parasite fails to develop in the mosquito and the patient becomes non-infective

List of drugs with Gametocytocidal activity:

1. quinine	2. mefloquine	3. chloroquine
4. artesunate	5. artemether	6. primaquine.

D. Drugs used for chemoprophylaxis:

These drugs (also known as ***causal prophylactic* drugs**) prevent malarial attacks through killing the parasite during the exoerythrocytic cycle and the erythrocytic cycle. True causal prophylaxis is not achievable with the present drugs, though vaccines may provide a future solution.

List of drugs used as chemoprophylactic: (used in combinations).

1. chloroquine	2. mefloquine	3. proguanil
4. pyrimethamine	5. dapsone	6. doxycycline

Chemoprophylactic agents are given to individuals who intend travelling to an area where malaria is endemic. Administration should start 1 week before entering the area and should be continued throughout the stay and for at least a month afterwards. No chemoprophylactic regimen is 100% effective and the choice of drug is difficult.

Examples of standard regimens (six different examples) of drugs used as prophylactic (Reference: *P.N Bennett, M.J. Brown 2008*):

1. Chloroquine 300mg (base) starts one week before travel at a dose of one tablet weekly.
2. Proguanil 200 mg once daily (start one week before travel)
3. Chloroquine + Proguanil
4. Malarone : one tablet daily (start 1-2 days before travel)

5. mefloquine + 250 mg once weekly (start one week before travel).
6. Doxycycline 100 mg once daily (start one week before travel)

Treatment of Malaria

A. Treatment of benign malaria:

Benign malaria is due to Plasmodium Vivax, Plasmodium Ovale and Plasmodium Malariae.

1. Chloroquine 600 mg (single dose), 6-8 hours later 300 mg
2. Second day 300 mg (single dose) chloroquine
3. Third day 300 mg (single dose) chloroquine.

Note: for Plasmodium Vivax and Plasmodium Ovale, Primaquine 15mg/day for 14-21 days started after chloroquine should be given for complete hepatic eradication of the parasite.

B. Treatment of P. Falciparum malaria:

It should be noted that most *P. Falciparum* are resistant to chloroquine. Treatment regimen as follow:

Quinine 600 mg every 8 hours for 7 days, followed by doxycycline 200 mg daily for at least 7 days. Doxycycline can be substituted by:

a. clindamycin 450 mg 4 times daily for 7 days
b. or Pyremethamine + Sulfadoxine (this combination is called Fansidar) 3 tablets as a single dose.

Individual antimalarial drugs:

1. **Chloroquine**

Mechanism of action of chloroquine

Chloroquine is a blood schizonticide. It acts by 2 possible mechanisms:

a. inhibiting the haem polymerase leading to accumulation of <u>haem</u> which is toxic to the parasite (as mentioned above).

b. Interfering with plasmodial DNA.

- Chloroquine it is usually given orally (half-life 50 hours) and it is concentrated in the parasite.
- less effective against P-vivax (*Lippincott's illustrated reviews, 3rd edition 2006*).
- has in addition antirheumatic, anti-amebiasis effects and in treatment of discoid lupus erythematosus.

Unwanted effects:

gastrointestinal disturbances, dizziness, urticaria, corneal deposit, headache; bolus intravenous injections can cause dysrhythmias. It should be used with caution in G6PD deficient patients (**<u>although haemolysis does not occur in every deficient patient</u>**).

2. Quinine
    - is a blood schizonticide.
    - Act by binding to plasmodium DNA to prevent protein synthesis.
    - It is given orally (half-life 10 hours) but can be given by intravenous infusion if necessary.

Unwanted effects include

gastrointestinal tract upsets, tinnitus (Cinchonism), blurred vision and, with large doses, dysrhythmias, hypoglycaemia and CNS disturbances. 'Black water fever' is very occasionally associated with its administration.

3. pyrimethamine ($t_{1/2}$= 4 days), a folate antagonist that acts as a slow blood schizonticide and is given orally).

4. dapsone ($t_{1/2}$= 24-48 h), a sulfone, given orally. or
5. Sulfadoxine ($t_{1/2}$= 7-9 days), a long-acting sulfonamide.
6. Proguanil ($t_{1/2}$ = 16 hours), a folate antagonist, is a slow blood schizonticide with some action on the primary liver forms of P. vivax. It is given orally.
7. Mefloquine is a blood schizonticidal agent active against P. falciparum and P. vivax. It is given orally and acts by inhibiting the parasite's haem polymerase. The onset of action is slow and the half-life is 30 days.
   The main unwanted effects are gastrointestinal disturbances, neurotoxicity (e.g. convulsions), and psychiatric problems.
7. Halofantrine ($t_{1/2}$ = 1-2 days) is a blood schizonticidal agent active against all species of malarial parasite, including multiresistant P. falciparum. It is given orally but absorption is irregular. Common unwanted effects (abdominal pain, gastrointestinal disturbances, and headache) are fewer than with mefloquine, but serious cardiac problems sometimes occur.
8. Primaquine (tissue schizonticide) is effective against the liver hypnozoites and is also active against gametocytes. Given orally, its half-life is 36 hours.

Mechanism of action:

It is not well understood however, metabolite of primaquine is oxidant and lethal to the parasite.

Unwanted effects are mainly gastrointestinal tract disturbances and, with large doses, methaemoglobinaemia. Haemolysis is produced in individuals with genetic deficiency of erythrocyte G6PD. Risk of hemolysis can be minimized by giving small doses once weekly and for longer duration.

9. **Artemisinin**: is a compound isolated from the leaves of Chinese herb. **Artesunate and artemether** are soluble derivatives of artemisinin, widely used in Asia and Africa but are not licensed in Europe or the USA. They are fast-acting blood schizonticidal agents. **Artemether** is lipid soluble (used as oral, IM, rectal) while artesunate is water soluble and can, in addition, be given intravenously. Side-effects are rare.

   Artesunate and artemether are usually given in combination:

   1. **riamet** = Artemether (20 mg) + lumefantrine (120 mg). Riamet is highly effective with a cure rate of 96% can be obtained. Riamet can be given for resistance uncomplicated *P. falciparum.*
   2. Artesunate + sulfadoxine-pyremethamine

41. Corticosteroids

The main reference:
Bennett et al (editors). Clinical pharmacology, Edinburgh …, Churchill Livingstone, Eleventh edition, 2012

Adrenal Steroids

1. Cortisol (Hydrocortisone, HC)

- a glucocorticoid with anti-inflammatory and also mineralocorticoid effects
- secreted by the largest middle zone of the adrenal cortex; the fasciculata

(cortisol is the endogenous hormone, HC is the exogenous drug)

Following adrenalectomy, 20-30 mg daily of hydrocortisone is usually required, given in two doses; the larger in the morning, and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion

2. **Aldosterone –** a mineralocorticoid (sodium-retaining), secreted by outer cortical zone; the glomerulosa
3. **A number of androgens and estrogens (sex hormones),** secreted by the inner cortical zone; the reticularis

In general, an adrenal steroid indicates a substance with hydrocortisone-like activity

The hypothalamus-pituitary system controls hydrocortisone secretion (and to a lesser extent aldosterone) through Corticotropin-releasing factor (CRF) and ACTH. Aldosterone secretion and synthesis is regulated mainly by the renin-angiotensin system and by variation in plasma potassium

Mechanism of steroid action

- Actions mediated through regulation of genes
- Actions not mediated by genes (non-genomic effects, e.g. inhibition of the release of the inflammatory PGE2, ..)

A) Actions mediated through regulation of genes

Transactivation of genes

GC binds to a receptor in the cytosol. After binding, the steroid-receptor complex translocate into the nucleus to bind to the target genes resulting in the gene expression (upregulated) to form proteins and enzymes that have a wide range of metabolic effects, e.g. enhancing the formation of a protein called lipocortin which inhibits phospholipase A2; the enzyme that releases arachidonic acid from phospholipids in cell membrane (thus, inhibits both cyclooxygenase and lipo-oxygenase pathways)

Transrepression of genes

in which the activated hormone-receptor complex prevents the transcription of targeted genes e.g. preventing the transcription of pro-inflammatory genes that regulate interleukins, chemokines, cytokines and others

Pharmacological Effects

(occur in doses higher than physiological doses)

Effects on organic metabolism

1. Carbohydrate metabolism:

- increased glycogenolysis
- increased gluconeogenesis

- decreased peripheral glucose utilization (insulin antagonism) resulting in hyperglycemia and sometimes glycosuria (latent diabetes becomes overt)

2. **Protein metabolism**

- decreased anabolism (i.e. decreased conversion of amino acids to proteins) while catabolism continues (negative nitrogen balance)

Results of the negative nitrogen balance:

- muscle wasting
- osteoporosis
- slow growth in children
- skin atrophy
- increased capillary fragility (bruising)
- striae
- delayed healing of peptic ulcer and of wounds

3. **Re-distribution and deposition of fat on shoulders, face, and abdomen, with wasting of extremities (trunkal or central obesity)**. The secretion of **leptin** (the appetite suppressant) is inhibited, which may lead to increased appetite.

4. **Inflammatory response is depressed**

(regardless of the cause; this is dangerous in case of infection). Neutrophil and macrophage functions and release of mediators are depressed.

5. **Allergic responses are suppressed.**

The inflammatory consequences of antigen-antibody interaction are inhibited. Lymphoid tissue is reduced

6. **CNS:** euphoria or psychotic states may occur (probably due to changes in CNS electrolyte)(confusion, irritability, delusion, suicidal thoughts, especially with high doses)

7. **Anti-vitamin D action**

Reducing hypercalcemia and increasing urinary calcium excretion (Formation of calcium stones)

8. Growth in children is reduced (Growth of new cells)

9. Suppression of HPA system

(complete suppression of adrenal cortex can occur by exogenous daily dose of hydrocortisone 40-80mg or prednisolone 10-20mg or by equivalent doses of other steroids). Suppression of HPA axis is greatest and most prolonged when corticosteroids are given at night. Dexamethasone, 1 mg at night, is sufficient to suppress corticotropin (ACTH) secretion for 24 h.

Recovery of adrenal function:

- Is quick after use of steroids for few days
- May take months after months of use
- May take years after years of use
- A steroid-suppressed adrenal gland continues to secrete aldosterone

Individual adrenal steroids

Hydrocortisone (cortisol)

Hydrocortisone in pharmacological doses, has both gluco- and mineralocorticoid actions. Hydrocortisone and cortisone, because of their high mineralo-corticoid activity, are not suitable for chronic disease suppression, but suitable for replacement therapy, and for emergency management of some conditions by i.v. route.

Hydrocortisone is preferred to cortisone because cortisone is inactive and requires conversion to hydrocortisone (cortisol) in the liver. Cortisone, therefore, is not active topically.

Prednisolone

Predominantly antiinflammatory (glucocorticoid) with little sodium-retaining activity. It is the standard steroid choice by mouth for long-term disease suppression.

Beclomethasone, Budesonide, fluticasone,…

Potent, soluble steroids, more marked topical effect than when given by mouth, suitable for use by inhalation for asthma and intra-nasally for hay fever. The swallowed part of the inhaled dose is largely inactivated by hepatic first pass metabolism (causing less systemic side effects and less HPA axis suppression)

Pharmacokinetics

- Well absorbed from the GIT and after i.m. injection
- Maximum biological effect occurs after 2-8 h
- Metabolized mainly in the liver
- highly protein bound (HC 95% bound)

Half-life is prolonged by liver and kidney disease and shortened by enzyme inducers.

Duration of action is short with hydrocortisone, intermediate with prednisolone and long with betamethasone and dexamethasone).

If a single daily dose is to be given, it should be given in the morning to coincide with the natural activation of the HPA axis (high HC level in the morning and low at evening).

Choice of adrenal steroids

- For oral replacement therapy: Hydrocortisone (as glucocorticoid) and fludrocortisone (as mineralocorticoid) are used.

- For antiinflammatory and antiallergic effect: Prednisolone or dexamethasone, and for inhalation: beclomethasone or budesonide, are used.
- For HPA suppression e.g. in adrenal hyperplasia; prednisolone or dexamethasone can be used.

Adverse effects of steroid therapy

Unwanted effects are unlikely if the daily dose is below 50 mg hydrocortisone or 10 mg prednisolone or equivalent doses.

1. Endocrine adverse effects

- Features of Cushing's syndrome (moon face, central obesity, edema, hypertension, striae, bruising, acne, hirsutism, diabetes may occur)
- HPA suppression with adrenal atrophy

HPA suppression is dependent on:

The type of corticosteroid used, its dose, the duration of use, and the time of administration (morning vs evening).

20 mg prednisolone in the morning may cause suppression, whereas only 5 mg late in the evening can cause suppression.

Substantial suppression can occur within one week

2. Mineralocorticoid side effects

Hypertension, sodium and water retention, potassium and calcium loss. These are probably none with triamcinolone, negligible with high potency glucocorticoids (dexamethasone, betamethasone), slight with prednisolone and methylprednisolone, and significant with hydrocortisone. triamcinolone**).**

3. Musculoskeletal

Proximal myopathy, tendon rupture, osteoporosis (leading to fractures), growth in children is impaired. Avascular necrosis of bone (particularly femoral heads) – a serious complication occurs at higher doses due to restriction of blood flow through bone capillaries.

4. Immune adverse effects

Suppression of inflammatory response to infection, and of the immune system (immunosuppression), which result in:

- Atypical signs and symptoms of inflammation
- Increased susceptibility to infection
- Spread of infection, clinical presentation may be atypical
- Candidiasis occurs; especially in GIT
- Dormant Tb may become active
- Live vaccines (e.g. measles, mumps, rubella, oral polio, BCG…) become dangerous

5. GIT adverse effects

Regular steroid taking especially with NSAIDs leads to more incidence of peptic ulcers and hemorrhage (perforation may be silent because of inhibition of signs and symptoms of inflammation)

6. CNS adverse effects

Euphoria

Depression and psychosis (during the first few days of high-dose administration)

Insomnia, suicidal thoughts,..

Aggravation of schizophrenia and epilepsy

Increased intracranial pressure with papilledema

7. Ophthalmic effects

Posterior subcapsular lens cataract

(risk occurs with prednisolone dose >10mg/day or equivalent for more than a year)

Glaucoma (with prolonged use of eye drops)

Corneal and scleral thinning

Spread of viral (e.g. herpetic) infection with perforation of corneal ulcers

8. Others

Menstrual disorders

Delayed tissue healing (myocardial rupture after MI)

Thromboembolism

9. Skin side effects

Thinning of the skin (skin atrophy), striae, acne, and hirsutism, delayed wound healing, and bruising

10. During pregnancy

Steroids are teratogenic in animals. No convincing evidence in human. Fluorinated steroids are more teratogenic; betamethasone and dexamethasone cross the placenta readily, while prednisolone and methylprednisolone are, mainly, inactivated as they cross the placenta (highly sensitive to the placental enzyme: beta-hydroxy steroid dehydrogenase type 2).

Labour is managed as for a major surgery (major stress) (50-100 mg hydrocortisone i.m. or i.v. every 6 hours for 24-72 h; then reduce dose by half every 24 h until normal dose is reached).

Clinical uses of corticosteroids

In inflammatory diseases and for immunosuppression (prednisolone is preferred)

e.g.- connective tissue disease such as SLE

- severe asthma
- acute lymphatic leukemia
- acquired hemolytic anemia
- severe allergic reactions (not used alone because they are not quick enough)
- organ trasplantation, …etc.

Adrenal steroids are also used in some cases of :

Rheumatoid arthritis, rheumatic fever, ankylosing spodylitis, ulcerative colitis, Chron's disease, allergic rhinitis, nephrotic syndrome, skin diseases (e.g. eczema), raised intracranial pressure, cancer, …

For replacement therapy in acute and chronic adrenocortical insufficiency.

For suppression of adrenocortical function (excess androgen secretion in congenital adrenal hyperplasia) by HC in children and HC or prednisolone or dexamethasone in adults).

Withdrawal of steroid therapy

"The longer the duration of treatment, the slower must be the withdrawal"

- If treatment for less than one week, withdrawal can be rapid
- Treatment for 2 weeks, dose is reduced by 50% every day

- Longer, particularly if repeated doses given in the evening or in high doses (>40 mg prednisolone); withdrawal should be very slowly (e.g. 2.5-5mg prednisolone or equivalent every 3-7 days)

Full recovery (response to stress) may take up to 2 years after the initial recovery.

Corticotropin (ACTH) should not be used to hasten recovery of the atrophied cortex since it further suppresses the HP axis.

Inhibition of synthesis of adrenal steroid hormones

Used in the control of excess production of corticosteroids e.g. tumors of pituitary or adrenal cortex, e.g. **Metyrapone** which inhibits 11 –beta-hydroxylase which is important in the synthesis of hydrocortisone and to a lesser extent aldosterone

Others: Trilostane (affect both cotisol and aldosterone), **aminoglutethimide** (inhibits all steroids; it inhibits conversion of cholesterol to pregnenolone), **ketoconazole, …**

	GC	MC	
Hydrocortisone (cortisol) 20 mg tab	1	1	Given orally, i.v. (as sodium succinate) and intra-ar acetate suspension)
Prednisolone 5 mg tablet	4*	0.8*	Is the standard choice for antiinflammatory therap i.m.
Methylprednisolone 4 mg tablet	5	Mini-mal	Similar to prednisolone, used i.v. for large dose the
Triamcinolone 4 mg tablet	5	None	Fluorinated corticosteroid, causes muscle wasting
Dexamethasone 0.5 mg tablet	30	Negligible	Suitable for high dose therapy where fluid retentio disadvantage. Powerful, long-acting, used for therapeutic adreno suppression.
Betamethasone 0.5 mg tablet	30	Negli-ible	
Fludrocortisone 0.1 mg tablet	15	150	Used instead of aldosterone for replacement therap choice in autonomic neuropathy
Aldosterone (not given orally)	None	500	Rapid oral inactivation Spironolactone is its competitive antagonist

42. Antidiabetic Drugs

Diabetes mellitus type 1 is due to insulin deficiency. Treatment is dietary modification plus insulin administration.

Diabetes mellitus type 2 is due to reduced secretion of insulin or insulin resistance (lack of sensitivity of target organs to insulin).Treatment is dietary modification with or without oral hypoglycemic agents and/or insulin.

I. INSULIN

Actions and effects:

It binds with and activates receptors on the cell membranes of most body cells. Target tissues are liver, muscle and adipose tissue. After insulin-receptors binding occurs, cell membranes become highly permeable and allow entry of glucose, amino acids, fatty acids and potassium. This results in the following effects:

1. reduction in blood glucose due to:

a) Increased glucose uptake in peripheral tissues (which oxidize glucose or convert it to glycogen or fat)

b) Decreased hepatic output of glucose by reducing glycogenolysis and gluconeogenesis.

1. anabolic effects :

- in muscles and most other cells, insulin facilitates amino acid uptake and their synthesis into proteins, as well as inhibits proteins breakdown so decreased amino acids output (precursors for hepatic gluconeogenesis).

-In adipose tissue insulin inhibits lipolysis and favors triglyceride synthesis.

2. Suppression of ketogenesis (ketone body synthesis) by: a) Inhibiting lipolysis, in adipose tissues, and release of free fatty acids; the major source for hepatic ketogenesis. b) Suppressing hepatic oxidation of free fatty acids to ketone bodies.
3. Stimulation of K^+ entry into cells, by stimulating Na^+/K^+ ATPase action.

Sources of commercial insulin preparations:

- Pork or beef pancreas.
- Human insulin: made either by enzymatic modification of porcine insulin or by using recombinant DNA technology e.x. soluble insulin
-human insulin analogues :made by modifying the amino acid sequence of the human insulin molecule to produce insulin preparations with different onset and durations of action but similar pharmacodynamics effects e.x. insulin lispro and insulin glargine.

Pharmacokinetics: Insulin cannot be taken orally because; it is a peptide and digested in GIT.

Main route of administration: subcutaneous but can be given IV and IM .

It is cleared out of circulation rapidly because of binding to peripheral tissues and metabolism in the liver, kidneys, muscles, and plasma and excreted by kidneys. The plasma t1/2 is 5-9 min.

Factors affecting subcutaneous absorption:

- Site: The abdomen has the fastest rate of absorption, followed by the arms, thighs, and buttocks.
- Massage of injection site, exercise and heat application increases absorption, probably by increasing blood flow to the skin.
- Areas of lipohypertrophy usually show slower absorption rate.

Dose and Daily insulin requirement in diabetics:

Daily pancreatic secretion is 30-40-units, and most insulin- deficient diabetics need 30-50 unit insulin per day. The standard strength (amount) of insulin in vials is 100 unit/ml.

Insulin preparations :

1) *Short- acting:* ex. **soluble insulin**:
   - clear solution
   - Onset of action is (30min after subcutaneous injection so, need to be injected 30minutes before the main meals to control the early postprandial hyperglycaemia.
   - Duration of action is (8 hrs.) thus requires frequent administration.
   - **Can be given i.v.: acts faster and can be given in high dose** for **treatment** of :
     a) ketoacidosis : Ketone bodies inhibit glucose uptake by brain and muscle
     b) Acute short term Insulin resistance (Insulin requirement increases > 200 U/day) due to infection, trauma, surgery, emotional stress; where corticosteroids and other hormones are produced in excess as a reaction to the stress and oppose insulin actions.
     c) Hyperkalaemia
2) *Rapid -acting insulin*: ex. **insulin lispro**
   - *Clear solution* of modified human insulin
   - Onset of action: very rapid (within 15 minutes) after subcutaneous injection; can be injected immediately before or even after the meal to control postprandial hyperglycaemia.

- Duration of action is 5 hours. This decreases the risk of late post meal hypoglycaemia.

3) Intermediate acting insulin: e.x. **NPH** (Neutral protamine Hagedorn) (isophane insulin)

- Cloudy neutral suspension of insulin with equivalent amount of Protamine, a basic protein that delays absorption and prolongs the duration of action of insulin.
- Onset of action is 1.5 hours and duration of action is 12 hours.

4) Long acting insulin: e.x. **insulin glargine**

- Clear solution, has an acidic pH. When administered subcutaneously, insulin precipitates at the neutral pH in tissues at injection site then dissociates slowly to enter the circulation. Onset of action is delayed (1.5) hrs. so, it does not control postprandial hyperglycaemia, but relatively a low peakless continuous blood levels of insulin are maintained for up to 24 hours. Thus it is suitable for once daily administration..
- Should not be mixed with other forms of insulin in same syringe to avoid disturbance of its pH and lose of efficacy.

5) Biphasic insulin: a premixed combination of fast and long- or intermediate - acting insulin ex. insulin mixtard that contain 30% soluble insulin plus 70% NPH insulin.

Side *effects*:

1. Hypoglycemia- If it is not treated it may progress to coma.
2. Lipodystrophy (*hypertrophy* or *atrophy*) of subcutaneous fatty tissues at injection site; can be prevented by advising the patient to change sites within the injection area.

3. Allergy as urticaria and anaphylaxis due to immune reactions to animal insulin preparations or additive proteins. Bovine insulin is more antigenic than porcine insulin.
4. Local reactions as swelling and erythema.
5. Insulin resistance due to antibodies against animal insulin or additive proteins. Insulin requirement may increase > 200 U/day. Switching to human insulin can reduce resistance.

II. <u>Oral Antidiabetic Drugs</u>

- Only effective for type 2 diabetes
- Require presence of endogenous insulin for their actions so; ineffective in type 1 diabetes .
- Ineffective during pregnancy- should be replaced by insulin
- Ineffective and should be temporarily replaced by insulin in acute conditions where insulin requirement is increased rapidly i.e. diabetic ketoacidosis and acute stress conditions as during surgeries, acute infections and myocardial infarction.

Classification:

(1) **Drugs that increase insulin secretion:**

a) **<u>Sulphonylureas:</u>**

Are Sulphonamide derivatives

Are taken orally before the main meals.

Are preferred in lean or ideal weight patients because they cause weight gain.

Promote insulin release …

Can cause hypoglycaemia in diabetic as well as in non- diabetic person.

<u>Mechanism of action</u>: They stimulate release of insulin from pancreas.

They act on pancreatic β cell membrane-- block the ATP-sensitive K^+

channels; this prevent K^+ exit which results in depolarization. This enhances Ca^{+2} entry; and the rise in intracellular Ca^{+2} enhances the rate of insulin secretion in response to rise in blood glucose level.

-After chronic administration they sensitize the target tissues (liver, muscle and adipose tissue) to the action of insulin by increasing the number of insulin receptors.

Classification:

1st generation agents ex. chloropropamide (withdrawn due to side effects), tolbutamide.

2nd generation agents have similar efficacy but they are more potent than 1st generation agents ex. glibenclamide, glipizide, glimepiride:

- Selection does not depend on potency but it depends on duration of action, side effects as well as patient's age, renal function and liability to develop hypoglycaemia.
- Long acting members as glibenclamide (glyburide) and glimepiride can be given once daily as well as they cause more incidence of late post meal hypoglycemia, so they are not preferred in elderly.
- Tolbutamide, gliclazide and glipizide have shorter duration of action…less risk of prolonged hypoglycaemia……more suitable in elderly.
- Glibenclamide is excreted by liver and kidney…… dose needs to be adjusted in patient with liver or renal impairment.
- Gliclazide ,glipizide and tolbutamide: are metabolized in liver to inactive metabolites before excretion by kidney ….safe in patient with impaired renal function.

Side effects:

- Hypoglycemia.

- ❖ Weight gain because insulin release stimulates appetite.
- ❖ Secondary failure after months or years due to declining of beta cells function and insulin resistance.
- ❖ Teratogenic in animals… avoid during pregnancy

b)Meglitinides ex. repaglinide, nateglinide

- Stimulate insulin release by a similar mechanism as sulphonylureas.
- Induce rapid very "short- lasting" insulin release. It is administered before each major meal to boost the postprandial insulin release and control postprandial hyperglycaemia.
- Because of short lasting action so lower risk of hypoglycemia.
- Metabolized in liver –should be avoided in liver impairment .

c)Incretin analogues ex. exenatide

Mechanism : an analogue of the endogenous glucagon-like-peptide 1 (incretin) that is secreted from upper small intestine in response to glucose and enhances postprandial insulin secretion, suppresses glucagon secretion, slows gastric emptying and decreases appetite).

used in overweight patients, given Sc, may cause nausea as a side effect

d)sitagliptin:, inhibits dipeptidyl peptidase-4 enzyme that is responsible for breakdown of GLP-1 and potentiate its action. It is administered orally**.**

(2) Insulin sensitizers (increase the sensitivity of target organs to insulin)

a)**Biguanides**: **ex.** *Metformin*

Mechanism of action: It prevents hyperglycaemia as it

1- Suppresses hepatic gluconeogenesis and glucose output.

2-sensetizes the target tissues (especially muscle) to the action of insulin so, enhances glucose utilization.

3-reduces intestinal absorption of glucose.

- ❖ Can be given after main meals
- ❖ does not cause hypoglycemia because it does not promote insulin release
- ❖ is excreted unchanged by kidneys and so may accumulate to toxic levels in renal impairment.
- ❖ does not cause weight gain so, it is preferred for overweight and obese patients having normal renal function.
- ❖ Other uses : treatment of polycystic ovary syndrome (a condition of insulin resistance that contributes to hyperandrogenism, hirsutism, menstrual disorders and infertility).

Side effects:

- *diarrhea*, anorexia, *nausea* and metallic taste
- ❖ lactic acidosis in patients with renal impairment or liver failure.
- Vitamin B12 deficiency (due to impaired absorption). Patient may need vitamin B12 injections periodically.

b)**Thiazolidinediones** (glitazones):

e.x. pioglitazone

Mechanism of action: sensitizes the peripheral tissues (especially fatty tissues) to the action of insulin by activation of certain genes.

-do not promote insulin release…..do not cause hypoglycemia.

- ❖ *Side effects*: fluid retention, peripheral oedema , weight gain .

(3) **Alpha glucosidase inhibitors:** e.x.. **acarbose**

Mechanism of action:

inhibits α- glucosidase enzymes, responsible for digestion of complex carbohydrate in small intestine, so prevents the postprandial rise in blood glucose.

- ❖ does not cause hypoglycemia.

- ❖ is taken just before main meals.
- ❖ Side effects: flatulence, diarrhea, abdominal pain and distension

Hypoglycaemia

Precipitating factors: missing a meal, unusual physical exercise, over dose of insulin or oral hypoglycaemic drugs and co-administration of drugs that intensify hypoglycaemia as salicylates, sulphonamides and cimetidine .

Warning signs: sweating, tremor, tachycardia and palpitation (Which drugs masking these symptoms and why?

Treatment:

- ➢ glucose must be given orally or i.v.(if the patient is unconscious)
- ➢ glucagon S.C. or I.M enhances glycogenolysis and increases hepatic glucose output, but in about 45 minutes from onset of coma the hepatic glycogen will be exhausted and glucagon will be useless.

43. Anti-thyroid drugs

Thyroid physiology

The thyroid gland produces three main hormones: tri-iodothyronine (T3) and thyroxine (T4-tetra-iodothyronine) and calcitonin (involved in the control of plasma calcium).

*T3 is more potent than T4

*Liothyronine is the synthetic T3 and levothyroxine is synthetic T4

Synthesis and fate of thyroid hormones

Formation of thyroid hormone begins with:

1. active transport of iodide into thyroid gland

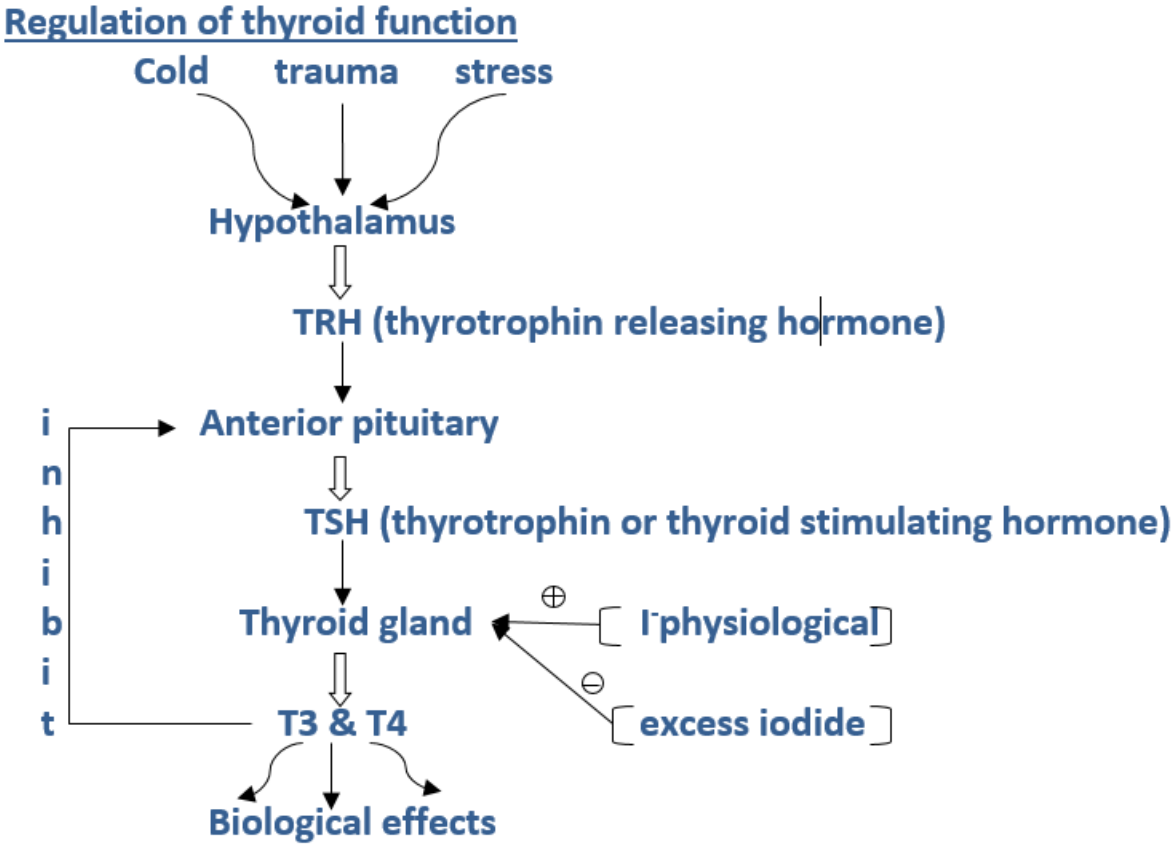
2. oxidation of iodide to iodine (the active form of iodide); which is catalyzed by thyroperoxidase enzyme

3. activated iodine is incorporated into tyrosine residues that are bound to thyroglobulin (a large glycoprotein molecule), resulting in formation of monoiodotyrosine (MIT) and diiodotyrosine(DIT)

4. coupling of iodinated tyrosine molecules takes place.

*coupling of one MIT with DIT ⟶ T3

*coupling of two DIT ⟶ T4



Fate Thyroid hormones are released from the thyroid gland by a proteolytic process. The amount of T4 released is greater than the amount of T3. However, much of T4 released undergoes conversion to T3 by enzymes in peripheral tissues.

*About 80% of T3 found in plasma is due to conversion of T4 to T3

*In blood both T3 and T4 are extensively (99.9%) bound to plasma proteins (thyroxine binding globulin TBG and thyroxine binding prealbumin TBPA)

***only the free circulating thyroid hormones produce biological effects**

*Both T3 and T4 are metabolized in liver which is slow, so half-lives of these hormones are prolonged, $t_{1/2}$ of T3 is 1.5 days and $t_{1/2}$ of T4 s 1 week.

*TSH acts on the thyroid gland causing increase in:

1. Gland size

2. Iodine uptake

3. Synthesis and release of thyroid hormones

*The rising plasma levels of T3 and T4 leads to suppression of TSH release.

Hyperthyroidism (Thyrotoxicosis) either:

1. Diffuse toxic goiter (Grave's disease)

2. Toxic nodular goiter (adenoma)

*The symptoms are due to supra-physiological amounts of thyroid hormones leading to tachycardia, nervousness, tremor, diarrhea, increase in skin temperature and sweating, marked sensitivity to heat (↑BMR), fatigability, increased appetite with weight loss.

Aim of treatment

To reduce excessive secretion of thyroid hormones by:

1. Subtotal thyroidectomy or radioactive iodine(^{131}I) to reduce amount of functioning thyroid tissue

2. Antithyroid drugs to decrease secretion of thyroid hormones

3. Symptomatic treatment with beta-blockers

Anti-thyroid drugs

A. Thionamides (Thiourea derivatives)

Carbimazole, Methimazole & Propylthiouracil

Methimazole is the chief metabolite of carbimazole.

Mechanism of action

1. Block thyroid hormone synthesis by:

a) preventing oxidation of iodide, so inhibiting incorporation of iodine into tyrosine

b) prevents iodinated tyrosine from coupling

*Both these effects due to inhibiting thyroperoxidase enzyme

2. Propylthiouracil also acts peripherally to suppress conversion of T4 to T3.

Note although propylthiouracil prevents thyroid hormone synthesis, it does not destroy existing stores of thyroid hormone, so once therapy begun, it may take 1-2 weeks for existing stores to become depleted.

Therapeutic uses

1. alone in Grave's disease
2. as an adjunct to radiation therapy
3. in preparation for thyroid surgery
4. propylthiouracil for thyrotoxic crisis (by inhibiting hormone synthesis and preventing conversion of T4 to T3).

Adverse effects are relatively rare; however severe adverse effects can occur:

a. Agranulocytosis is the most serious toxicity, usually occurs during first 2 months of therapy. Sore throat and fever may be the earliest symptoms, so patients should be instructed to report these immediately and repeated blood counts should be done.

If agranulocytosis occurs, the drug should be discontinued and treatment with granulocyte-colony stimulating factor may accelerate recovery.

b. Hypothyroidism due to excessive dosing

c. Others rash, nausea, arthralgia, headache, dizziness and parasthesia.

Thionamides in pregnancy & lactation

If a pregnant woman has hyperthyroidism, she should be treated with the smallest possible amount of these drugs because they cross the placenta, overtreatment causes fetal goiter.

*Surgery in the second trimester may be preferred to continued drug therapy.

*They are safe in lactating woman but because of the risk of hepatotixicity, carbimazole is preferred.

B. Radioactive iodine (^{131}I)

*Is the first line treatment particularly in USA.

Is concentrated in thyroid gland. Destruction of thyroid tissue is produced primarily by emission of beta particles. Since beta particles have a very limited ability to penetrate any type of physical barrier, these particles do not travel outside the thyroid, so damage to surrounding tissue is minimal.

*Reduction of thyroid function is gradual. Initial effects become apparent in days or weeks. Full effects develop in 2-3 months.

Uses is usually given for middle-aged and elderly patients

1. In Grave's disease
2. In thyroid cancer- high doses are required
3. For diagnosis of a variety of thyroid disorders

Advantages

*Easy administration (orally in solution as sodium ^{131}I, given as one single dose)

*Low cost

*Patients are spared the risks, discomfort and expense of thyroid surgery

*Death due to ^{131}I had never occurred

*No tissue other than thyroid is injured

Disadvantages

* Delayed effect (for 1-2 months)

*Delayed hypothyroidism

*Theoretical risk of thyroid cancer

Contraindications

1. Children-risk of delayed hypothyroidism is higher than in adults
2. Pregnancy-after first trimester, it may damage:
    - ✓ the immature thyroid
    - ✓ it causes generalized developmental harm during whole pregnancy.
3. Breast feeding

C. Iodide products (Non-radioactive) include:

1. Strong iodine solution (lugol's solution)
2. Sodium iodide
3. Potassium iodide

*All have same mechanism of action and similar pharmacological effects.

Lugol's solution

Is a mixture of elemental iodine and potassium iodide

Mechanism of action it suppresses thyroid function by:

1. Decreasing iodine uptake, suppressing both the iodination of tyrosine and coupling of iodinated tyrosine
2. Inhibiting release of thyroid hormone into blood stream

*With long term iodide administration, suppressant effects become weaker, so iodide is rarely used alone to produce thyroid suppression.

Therapeutic uses

1. In preparation for surgery
2. Thyrotoxic crisis
3. As antiseptic
4. As expectorant
5. As contrast media in radiology

Adverse effects

Chronic ingestion of iodine causes iodism characterized by: metallic taste, burning sensation in mouth &throat, soreness of teeth & gums, frontal headache, coryza (nasal inflammation & sneezing), various skin eruptions, excessive salivation with painful salivary gland.

Overdose

Iodine is corrosive and overdose will injure GIT, causing abdominal pain, vomiting & diarrhea.

D. Beta- blockers

β-blockers without intrinsic sympathomimetic effect (ISA) like propranolol, cause clinical improvement of hyperthyroid symptoms but do not alter thyroid hormones level, so they are not used as a sole therapy.

Uses

1. in patients on long wait for effect of antithyroid drugs
2. in preparation for surgery
3. as a part of treatment of acute hyperthyroid crisis

44. (1) Antidiuretic Hormone (vasopressin) preparations

Vasopressin:

-is synthetic structurally similar drug to the natural ADH

-can be administered SC, IM or IV.

-duration of action short (2-8 hrs.) because it is metabolized by tissue peptidase.

mechanism of action: It has a potent V1 but weak V2 agonist activity.

- stimulates V1 receptors on smooth muscle of blood vessels and GIT . This results in an increase of intracellular calcium concentration which results in contraction of all smooth muscle of GIT and powerful vasoconstriction.
- Weakly Stimulates V2 receptors resulting in antidiuretic effect (similar mechanism as desmopressin)

Uses: 1- postoperative abdominal distension 2- before abdominal radiography to dispel gases from bowel3- Bleeding oesophageal varices.

4-neurogenic diabetes insipidus

side effects::

1-increased arterial pressure, angina , MI, peripheral ischemia and gangrene, due to vasoconstriction.

2-abdominal cramps and intestinal colic

Terlipressine

-is a prodrug of vasopressin .It is a selective V_1 agonist

Uses: intravenously for bleeding esophageal varices.

Side effects: similar to vasopressin

Felypressin:

-is a selective V_1 agonist

-has short duration of action,

Uses: with the local anesthetic to prolong their effects due to its vaoconstricting action (It does not raise blood pressure and preferable to adrenalin in hypertensive patient).

Desmopressin:

-is a structural analogue of vasopressin with no vasopressor effect

-has a long duration of antidiuretic action (8-20h) (because enzymatic degradation is slow) allowing once or twice daily administration.

-Can be administered orally, sublingually, intranasal spray, subcutaneously and intravenously.

Mechanism: It selectivelyactivatesV2 on the collecting duct cells in the kidney. This stimulates adenylcyclase ⟶ increasing cAMP production, which results in increasing of their water permeability due to opening of additional aqueous channels‘ aquaporins’ that allow more water reabsorption.

Uses

1-Drug of choice for neurogenic diabetes insipidus.

2-nocturnal enuresis (bed wetting) i.e. in child > 5 years.

3- Bleeding in hemophilia and von Willebrand's disease by releasing factor VIII and von Willebrand's factors; due to activation of (extra renal V_2-like receptors) in vascular endothelial cells.

Side effects: excessive water intake can cause water retention, dilutional hyponatremia and water intoxication can progress to convulsions and coma. Patient should be instructed to reduce their accustomed water intake once ADH therapy is started.

Lypressin:

-V2 agonist

-Has short duration of action (3-8h)

-is administered intranassally

Uses: neurogenic diabetes insipidus

Alternative drugs for diabetes insipidus:

Neurogenic diabetes insipidus: chlorpropamide (antidiabetic), carbamazepine (anticonvalsant)

Nephrogenic diabetes insipidus : thiazide diuretics

44. (2) Drugs Acting On the Uterus

Oxytocic drugs: stimulate the uterine contraction especially at term.

EXAMPLES:

A. oxytocin: (Syntocinon):

Pharmacological actions

1- Pregnant uterus: It increases the force and frequency of uterine contractions. In therapeutic doses , the contraction is slow, rhythmic with full relaxation in between(mimics uterine contraction of the normal labour), allowing placental blood vessels refilling which avoids fetal asphyxia .

Estrogens sensitize the uterus to oxytocin by increasing the number of oxytocin receptors.

Sensitivity increases progressively in third trimester and there is a sharp increase at term (immediately before the birth of the infant).

2-Breast: contracts myoepithelium causing milk ejection in lactating mother in response to suckling.

PKS: It does not given orally because as it is digested in GIT. It is administered as: intramuscular injection or intravenous infusion. Onset of action (2) minutes. The intensity of action can be controlled by the rate of the infusion and action can be quickly terminated because of its short half- life (6 minutes). Dose is designated as units /ml.

Uses:

1-Induction of labour

2- Uterine Inertia (slowly progressing labour)

3- To expel uterine contents in 2nd trimester incomplete abortion.

4- postpartum hemorrhage immediately after delivery; with or without ergometrine ; particularly in hypertensives in whom ergometrine is contraindicated.

5- to enhance milk ejection as nasal spray, before infant feeding,

Adverse effects: mostly due to high doses or rapid intravenous infusion :

1-tetanic contractions with rupture of uterus or fetal distress, asphyxia and fetal death. Infusion rate should be kept slow and duration of uterine contractions and fetal heart rate should be monitored throughout the infusion period.

2-Water intoxication because of (ADH) like action.

3-Hypotension due to vasodilating action.

Contraindications:

Cephalopelvic disproportion, fetal malpresentation, previous caesarian section and fetal distress

B. Ergot alkaloids:

Ergometrine (ergonovine) and **Methylergometrine (**a synthetic derivative of ergometrine but it is one and a half times more potent than it).

- can be given orally, IV and IM; acts almost immediately after IV injection, effect lasts for 3-hours.
- **Mechanism**:

They contract the gravid uterus at all months of pregnancy. The uterus is more sensitive at term and early puerperium. The uterotonic action is due to partial agonist action on 5 Ht2 and α1 adrenergic receptors. The contractions are fast, sustained **and tonic,** superimposed on normal myometric contraction and do **not followed by relaxation** thus, *they are **not used for induction of labour** because of **risk of fetal***

Differences between Ergometrine and Oxytocin

Parameters	**Ergometrine**	**Oxytocin**
receptors	α, dopamine and 5HT2 agonist	Oxytocin receptors agonist
Nature	Alkaloid	Peptide
Route	Oral, IM and IV	Mostly IV
Effect on pregnant uterus	Faster tonic contraction without relaxation	slow rhythmic contraction with full relaxation in between
Time of administration	After the 3rd stage of labor(just after the birth of the child)	1st stage
Main clinical use	Post-partum haemorrhage	Induction of labour
Milk ejection	Does not help	Helps

asphyxia *due to closure of placental blood vessels. On the other hand they are considered* as drugs **of choice for post-partum haemorrhage** because the sustained uterine contractions compresses the blood vessels and stop bleeding.

Uses:

1-Treatment and prevention of postpartum hemorrhage.

2- Management of incomplete abortion

3- to minimize postoperative blood loss at time of surgical evacuation (curettage) of the uterus

4- after delivery or cesarean section to ensure normal involution of uterus.

Side effects:

- Hypertension, paraesthesia of fingers and toes ,chest pain and angina due to vasoconstriction action
- nausea, vomiting (due to stimulation of D2 receptors),

Contraindications:

Uterine inertia during labor, pregnancy, hypertension, preeclampsia, peripheral vascular diseases.

Prostaglandins analogues:

$PGF_{2\alpha}$ (Dinoprost and Carboprost) , PGE_2 (Dinoprostone) and PGE1 (**Gemeprost** and **misoprostol**)

Contract non-pregnant as well as pregnant human uterus. Sensitivity is higher during pregnancy and increase with progress of pregnancy . In later part of pregnancy they also cause ripening (softening) of cervix.

USES:

1- Induction of abortion in 1st and 2nd trimester.

2- expulsion of uterine contents in missed , incomplete abortion and hydatiform mole .

3-Induction and augmentation of labour

4-post-partum haemorrhage, uncontrolled by oxytocin and ergometrine

5-cervical softening before labour

Side effects: vomiting, diarrhea, headache, fever, cervical laceration hypertension, asthma, pulmonary oedema

(Tocolytics) = uterine relaxants

Use:

1- premature uterine contractions to prevent pre-term labour ex. Salbutamol, Nifedipine

2- dysmenorrheal e.x. mefenamic acid, hyoscine N butyl bromide

45. (1) Oral Contraceptives

Are drugs that decrease fertility mainly by preventing ovulation

Oral contraceptive drugs are of two types:

1. Combined oral contraceptive pills
2. Progestogen only pills

Combined oral contraceptive pills

Is a combination of estrogen (ethinylestradiol, mestranol) and progestogen(2^{nd} generation like norethisterone, levenorgestrel or 3^{rd} generation like desogestrel, gestodene, and norgestinate)

These drugs are defined as second or third generation by progestogen component, the first generation is obsolete.

The pills are either:

a. Monophasic- contains a fixed amount of estrogen and progestogen given over 21 days.

b. Biphasic and triphasic-contain constant doses of estrogen and increasing doses of progestogen, given over 2 or 3 successive 7 –day periods (to achieve effective contraception with minimal distortion of natural hormonal rhythm)

*The pill started on first day of menstrual cycle (first day of menstruation) and continued for 21 days, followed by a period of 7 days when no pill is taken during which withdrawal bleeding occurs

*For easy compliance, some combined pills are packaged so that the woman takes one pill daily without interruption (21 active and 7 dummy)

*The pill should be taken at about the same time (to within 12h) every day to establish a routine

Mechanism of action

1. The principal mechanism is inhibition of ovulation through suppression of LH surge by hypothalamus and pituitary
2. Alteration of endometrium, so that implantation less likely to occur
3. Cervical mucus becomes more viscous and impedes the passage of **sperms**

Benefits of combined contraceptive pills additional to contraception

1. Decrease the risk of functional ovarian cysts, of ovarian and endometrial cancer and of benign breast disease
2. Decrease the risk of uterine fibroids and less bleeding
3. Regulation of menses with reduction of blood loss, less premenstrual tension and dysmenorrhea
4. For acne in young women (in combination with cyproterone)

Adverse effects

Are mainly due to estrogen component

1. Major

breast discomfort, fluid retention, headache (worsen migraine), nausea and rarely vomiting, lethargy, abdominal discomfort, vaginal discharge or dryness

2. Cardiovascular

thromboembolism, hypertension, increased incidence of myocardial infarction, cerebral and coronary thrombosis

3. Carcinogenicity

increase risk of breast and cervical carcinoma and of hepatoma

4. Metabolic

abnormal glucose tolerance (peripheral effect decreasing action of insulin), weight gain (with norethisterone derivatives)

5. Serum lipids

estrogen increases HDL and decreases LDL, while potent progestogen (like norgestrel) causes greatest increase in LDL:HDL ratio

6. Effect on menstruation

some will have intermenstrual bleeding

Contraindications

Absolute

1. History of thromboembolic disease
2. Transient ischemic attacks without headache
3. Infective hepatitis
4. Migraine
5. Past or present carcinoma of breast or genital tract
6. Undiagnosed vaginal bleeding
7. Smoking>40 cigarettes/day with age>35y

Relative (i.e. use with caution)

1. Family history of thromboembolism
2. Diabetes mellitus
3. Hypertension (less than 160/100 mmHg)
4. Smoking> 40 cigarettes /day
5. Age>35y
6. Obesity
7. Breast feeding

Drug interactions

1. Enzyme inducers- will cause breakthrough bleeding or unwanted pregnancy
2. Broad spectrum antimicrobials – ampicillin reduces efficacy of contraceptive pills by diminishing bacterial flora (that metabolize

ethinylestradiol in the large bowel and make it available for enterohepatic recycling)

Missed pill

1. If an omitted dose is remembered within 12h, it should be taken at once and the next dose at the usual time

2. If more than 12h have elapsed, it should be taken at once with the next dose at the usual time but additional barrier method of contraception should be used for 7 days

Progestogen only contraception

Is indicated

1. when estrogen is contraindicated

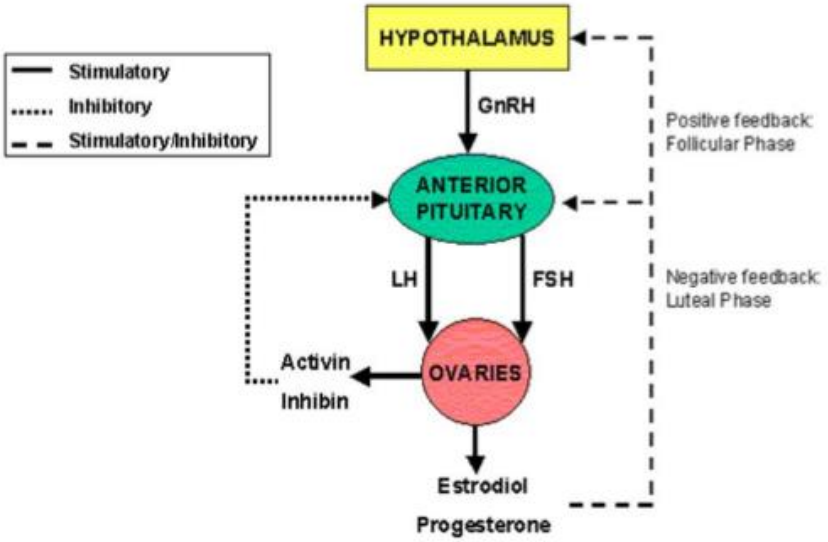
2. In lactating women

Mechanism of action

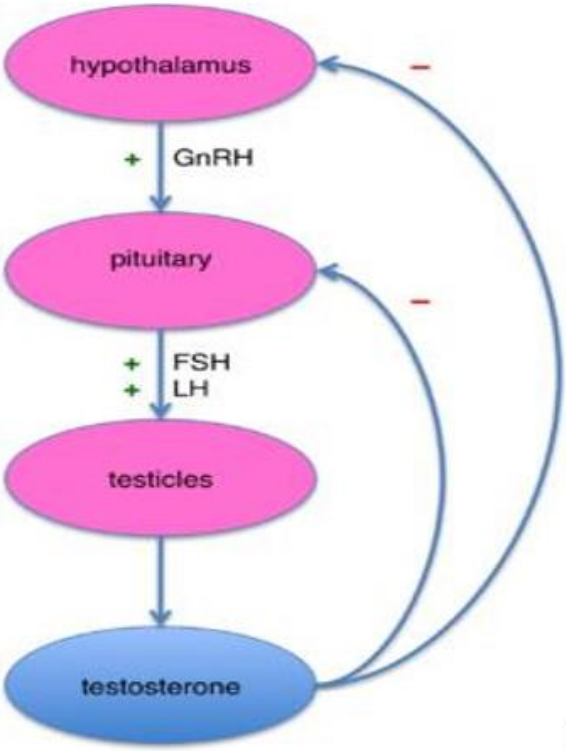
Progestogens render cervical mucus less easily permeable by sperms and induce premature secretory changes in endometrium so that implantation does not occur

45. (2) Sex Hormones

Sex hormones are secreted from gonads both in male (androgens) and female (estrogens and progestogens) under the control of gonadotrophin releasing hormone (GnRH); secreted from hypothalamus; which stimulates anterior pituitary gland to release gonadotrophins (follicle stimulating hormone; FSH and luteinizing hormone; LH).



In female



In male

Estrogens

Estrogens are required for the normal sexual maturation and growth of the female; they stimulate the development of vagina, uterus and uterine tubes as well as the secondary sex characteristics.

Two types of estrogens:

1. Naturally occurring- estradiol (the most potent and the major product of the ovary), estrone and estriol (less potent)

2. Synthetic estrogens- ethinylestradiol, mestranol undergo less first pass metabolism than the natural estrogens, so are effective orally.

Mechanism of action

After dissociation from their binding sites on sex hormone-binding globulin or albumin in plasma, they diffuse across cell membranes and bind with high affinity to specific estrogen nuclear receptors (α and β) which mediate the effects of the hormone.

Pharmacokinetics

Estrogens are readily absorbed through GIT, skin and mucus membrane.

Estradiol is rapidly metabolized compared with ethinylestradiol .

Estrogens are fat soluble, so are stored in adipose tissue from which are slowly released.

They are excreted in bile and reabsorbed through entero-hepatic circulation. Inactive products are excreted in urine.

Synthetic estrogens have longer duration of action and higher potency than natural estrogens.

Routes of administration

Oral, transdermal patch or gel, subcutaneous implants (release hormone over several months), vaginal (ring, cream, pessary) and nasal spray.

Therapeutic uses of estrogens

1. For contraception
2. Replacement therapy

a. postmenopausal -lowest effective dose for the shortest possible time, to relieve vasomotor symptoms like hot flushes, sleeplessness and vaginal dryness

b. premenopausal patients who are deficient in this hormone e.g. in premature or surgical menopause

3. Prevention and treatment of osteoporosis (but nowadays alendronate is considered as first line therapy)
4. Primary hypogonadism
5. Senile vaginitis (as pessary or cream)
6. Menstrual disorders
7. Androgen dependent carcinoma of prostate

Adverse effects

1. nausea and breast tenderness (most common)
2. headache, peripheral edema and hypertension
3. postmenopausal uterine bleeding
4. Increased risk of thromboembolism, gall stones, breast and endometrial cancer

Anti-estrogens and selective estrogen-receptor modulators

They interact with estrogen receptor but have different effects on different tissues (i.e. they are agonists or antagonists according to tissue type).

1. Clomiphene

Acts as a partial estrogen agonist, interferes with negative feedback of estrogens on hypothalamus, so increases the secretion of GnRH and gonadotrophins, leading to stimulation of ovulation

Is used in infertility associated with anovulatory cycles

Side effects: headache, nausea, vasomotor hot flushes, visual disturbances and ovarian enlargement

*Multiple ovulations and multiple pregnancies occur

2. Tamoxifen

Competes with estrogen for binding to estrogen receptor in breast tissue, **so used in** palliative treatment of metastatic breast cancer in postmenopausal women

Side effects: hot flushes and nausea, menstrual irregularity and vaginal bleeding, may cause endometrial hyperplasia and malignancies due to its estrogenic activity in endometrium

3. Raloxifene

Its **clinical use** in prevention and treatment of osteoporosis in postmenopausal women is based on its ability to decrease bone resorption and overall bone turnover. Bone density is increased and vertebral fractures are decreased.

*It has little or no effect on endometrium

Side effects: hot flushes and leg cramps are common, increased risk of DVT and pulmonary embolism

Progesterone and proestogens (Progestins)

Progesterone ($t_{1/2}$=5 min) is the natural progestin, is produced in response to LH in both females (secreted by corpus luteum during the 2nd half of menstrual cycle and by placenta) and in males (secreted by testes)

In female it converts uterine epithelium from proliferative to secretory phase that can accommodate implantation of the newly formed embryo
The high levels of progesterone during the luteal phase inhibit production of gonadotrophins and prevent further ovulation
*If conception occurs, progesterone continues to be secreted maintaining endometrium in a favorable state for continuation of pregnancy and reducing uterine contractions
*If conception does not take place, the release of progesterone ceases abruptly, which stimulates the onset of menstruation?

Progestogens are of two types:

1. Progesterone and its derivatives (dydroprogesterone, hydroxyprogesterone, medroxyprogesterone)
2. Testosterone derivatives (norethisterone, levonorgestrel, desogestrel, gestodene)

Pharmacokinetics

Progesterone is taken orally, well absorbed, has short half-life and completely metabolized by liver
Synthetic progestins are less rapidly metabolized
Duration of action of progestins lasts for 1-3 days while of medroxyprogesterone for 3 months ($t_{1/2}$=28h)

Preparations

1.Oral- norethisterone, levonorgestrel, dydrogesterone
2.Pessaries- progesterone
3.Injectable- progesterone, hydroxyprogesterone, medroxyprogesterone

Clinical uses

1. For contraception
2. Postmenopausal hormone replacement therapy

3. Dysfunctional uterine bleeding

4. Dysmenorrhea

5. Endometriosis

Adverse effects

Headache, depression, weight gain and changes in libido

The testosterone derivatives have androgenic activity causing hirsutism

Injectable medroxyprogesterone is associated with increased risk of osteoporosis (so duration of use should be limited)

Other progestogen derivatives

1. Danazol (Danol)

Is a derivative of progestogen, ethisterone. It has partial agonist androgen activity, but little progestogen activity.

Mechanism of action

It is a selective inhibitor of pituitary gonadotrophin secretion (FSH & LH) affecting the surge in the mid-menstrual cycle more than basal secretion. This reduces ovarian function, which leads to atrophic changes in endometrium both uterine and elsewhere (ectopic) i.e. endometriosis. In males it reduces spermatogenesis.

Uses

1. Endometriosis

2. Fibrocystic mastitis

3. Gynecomastia

4. Precocious puberty

5. Menorrhagia

6. Hereditary angioedema

Side effects

Virilization, acne, hirsutism

Antiprogestogens

Mifepristone

Is a competitive antagonist with partial agonistic activity

It is safe and effective in termination of pregnancy and efficacy is enhanced if its use is followed by vaginal administration of gemeprost to produce uterine contraction

Androgens

Are group of steroids that have anabolic &/or musculinizing effects in both males and females.

The most important androgen in human is testosterone; which is synthesized by leydig cells in testes.

Androgens are required for:

1. Normal maturation in male
2. Sperm production
3. Increased synthesis of muscle proteins and hemoglobin
4. Decreased bone resorption

Mechanism of action

Testosterone binds to specific nuclear receptor in target cells. It is active in liver and muscle, but in other tissues like prostate, seminal vesicle, epididymis and skin; it should be converted by 5α-reductase to dihydrotestosterone (DHT; the active metabolite) which binds to the receptor.

Pharmacokinetics

Testosterone is ineffective orally (because of the first pass metabolism), so it is administered i.m., as transdermal patch, topical gel, and buccal tablets are also available.

Testosterone derivatives (fluoxymesterone, oxandrolone) are given orally.

Example of anabolic steroids-nandrolone (taken by deep i.m. injection every 3 weeks)

Therapeutic uses

1. Androgenic effect-for primary and secondary hypogonadism

2. Anabolic effect: anabolic steroids are used in:

a. senile osteoporosis (because it prevents Ca^{+2} and nitrogen loss in urine)

b. chronic wasting associated with HIV or cancer

c. severe burns

d. to speed recovery from surgery or chronic debilitating disease

e. some patients with aplastic anemia

3. Endometriosis- Danazol

4. Unapproved use by athletes and body builders to increase lean body mass, muscle strength and endurance

Adverse effects

1. In female

Musculinization, acne, hirsutism, deepening of voice, menstrual irregularities

2. In male

Impotence, decreased spermatogenesis and gynecomastia, also stimulates growth of prostate

3. In children

Abnormal sexual maturation and growth disturbances resulting from premature closure of epiphysis

4. General effects

Elevation of serum LDL and reduction of HDL, so increase the risk of coronary heart disease, also causes fluid retention leading to edema

5. In athletes

cause premature closure of epiphysis, so stunts the growth and interrupts development

*High doses taken by young athletes result in reduction of testicular size, hepatic abnormalities, increased aggression and major mood disorders

Antiandrogens

Act either by:

1. interference with synthesis of androgens, or
2. blocking their receptors

1. Cyproterone (a derivative of progesterone)

It competes with testosterone for receptors in target peripheral organs, so reduces spermatogenesis even to the level of azoospermia, abnormal sperms occur during treatment. It also competes with testosterone in CNS causing impotence

Uses: a. to reduce male hypersexuality

b. prostatic cancer

c. severe female hirsutism and severe acne

2. Flutamide – is a competitive inhibitor of androgen in target cell, used in prostatic carcinoma

3. Finasteride- is used in benign prostatic hypertrophy because it inhibits 5α-reductase , so reduces production of dihydrotestosterone in prostate, therefore decreases prostate size

4. Ketoconazole- interferes with androgen and corticosteroid synthesis, so used on prostatic carcinoma and Cushing's syndrome

5. Spironolactone- may help hirsutism in women

46. Cancer Chemotherapy

(Cytotoxic Drugs)

There are **six** methods to treat cancer:

1. Surgery
2. Radiotherapy
3. Chemotherapy
4. Endocrine therapy
5. Biological therapy
6. Immunotherapy

Benefit achieved with cytotoxic chemotherapy:

- **Chemosensitive cancers(could be curable)**

  e.g. seminoma, teratoma, high grade non-Hodgkin's lymphoma, Hodgkin's lymphoma, Wilms' tumour

- **Chemoresistant cancers**

  e.g. gastric cancer, pancreatic cancer, sarcoma, hepatoma, melanoma, renal cancer, bladder cancer

Cell cycle phases:

Mitosis (Division)

G1: 1st gap (resting) phase (preparing)

S phase: DNA synthesis

G2: 2nd gap phase (repair)

Mitosis

In general, cytotoxics are most effective against actively dividing cells, and least effective against resting cells.

Cytotoxic drugs can be:

a) Cell cycle *non-specific*: kill cells whether resting or actively cycling e.g. alkylating agents, doxorubicin (cytotoxic antibiotic)

b) Cell cycle (phase) *specific*: kill only cells that are actively cycling e.g. antimetabolites, vinca alkaloids

Anticancer Drugs

- Alkylating drugs
- Antimetabolites
- Antibiotics (cytotoxic antibiotics)
- Alkaloids of plant origin (vinca alkaloids)
- Adrenocorticosteroids, hormones, their antagonists and many others

Alkylating Agents

(Nitrogen mustards and ethyleneimines)

- Act by transferring alkyl groups to DNA, usually in the N-7 position of guanine during cell division forming covalent linkage between two guanines on the a single DNA strand or cross-link two DNA strands preventing their replication. The same can occur with RNA or between DNA and proteins.
- **Examples**: cyclophosphamide, ifosfamide,
  chlorambucil, melphalan, busulfan,
  mustine (mechlorethamine),
  nitrosureas (carmustine **[BCNU] and lomustine [CCNU])**
  thiotepa

Cyclophosphamide

- Not itself cytotoxic, metabolized in the body by the liver to other alkylators; the main active metabolite is phosphoramide mustard.
- Given orally or i.v.
- Plasma half-life 6-12 hours

- Renal excretion of the more polar metabolite (Acrolein) results in irritation of the bladder and chemical (hemorrhagic) cystitis

Adverse effects

- nausea and vomiting
- alopecia (marked in the young)
- cystitis (drink plenty of fluids and empty bladder frequently; this urothelial toxicity is antagonized by mesna)
- myelosuppression at 7-10 days
- significant infertility in both males and females

Urothelial toxicity commonly manifests as hemorrhagic cystitis, and is peculiar to the use of cyclophosphamide and ifosfamide and caused by their metabolite: acrolein

Mesna (mercaptoethanesulphonate) provides free thiol groups that bind acrolein. High urine volume and mesna are used to prevent hemorrhagic cystitis particularly when high doses of cyclophosphamide and ifosfamide are used.

Antimetabolites

- Are structural analogues of normal metabolites required for cell function and replication and act by competition

Examples

- methotrexate: folic acid antagonist
- 6-mercaptopurine (6-MP): purine analogue
- cytarabine and 5- fluorouracil: pyrimidine analogues

- Antimetabolites cause GI toxicity including stomatitis and diarrhea as well as bone marrow depression

- Hepatic dysfunction potentiates the toxicity of 5-flurouracil since it is metabolized by the liver.
- 5-fluorouracil has been used in treatment of solid tumors including GIT tumours, and can be used topically for malignant skin lesions

Methotrexate (MTX)

- Is a folic acid antagonist; competitively inhibits the enzyme (dihydrofolate reductase) preventing the synthesis of tetrahydrofolic acid (folinic acid) which is essential for the synthesis of purines and pyrimidines and therefore nucleic acids.

Folinic acid rescue: folinic acid may be given 24 hours after large dose of MTX to bypass and terminates MTX action (bone marrow cells recover better than tumour cells; useful selectivity. It also protect against GI toxicity such as stomatitis and diarrhea)

- MTX can be given orally, i.v., i.m., and intrathecally
- It should be used with extreme caution in renal impairment as the kidney is its main route of excretion
- Active secretion of MTX by renal tubules is blocked by salicylates and probably other NSAIDs which also displace MTX from plasma proteins increasing risk of toxicity

Cytotoxic Antibiotics

-Interfere with DNA and/or RNA synthesis. **Examples**:

Bleomycin

The cytotoxic effect of bleomycin appears to be due to oxidative damage to DNA, leading to single and double stranded breaks.

Bleomycin is concentrated in skin and lung tissue and has a significant cutaneous and pulmonary toxicity. On the other hand, it has only mild myelo- and immunosuppressant activities

Doxorubicin (Adriamycin)

Others e.g. mitomycin and streptozotocin (the latter is used to treat islet-cell pancreatic tumours)

Alkaloids of plant origin

(Vincristine, vinblastine, vindesine)

- Inhibit microtubule assembly and cause cell cycle arrest in mitosis (spindle poisons)
- **Vincristine** causes peripheral neuropathy and minimal bone marrow suppression; **vinblastine** causes marked bone marrow suppression and minimal peripheral neuropathy

Other cytotoxic drugs

- Asparaginase
- Procarbazine
- Dacarbazine
- Platinum drugs e.g. cisplatin and carboplatin. They also cross-link DNA. Cisplatin can cause severe vomiting, nephrotoxicity and ototoxicity.
- Hydroxyurea
- Protein kinase inhibitors e.g. Axitinib
- Many others

Adverse effects of cytotoxic drugs

Cytotoxic drugs act against all cells which are multiplying rapidly:

Bone marrow, mucosal surfaces (gut), hair follicles, reticuloendothelial system, germ cells.

All dividing more rapidly than many cancers, and are also damaged by cytotoxic drugs.

Many solid tumours divide slowly and recovery from cytotoxic agents is slow, while normal marrow and gut recover rapidly. This rapid recovery is used as a basis for intermittent courses of chemotherapy.

Main adverse effects of cytotoxic drugs

- Nausea and vomiting
- Bone marrow suppression: bleeding, infection
- Gut epithelium and other mucosal surfaces: diarrhea, mouth ulcers
- Hair follicles: alopecia
- Germ cells and reproduction: sterility, teratogenesis
- Delayed wound healing
- Local toxicity if extravasation occurs
- Hyperuricemia
- Specific organ damage
- Second malignancies

Nausea and vomiting

- Common and can be severe
- May be immediate (within 1-5 hours), or delayed for several days (it could be anticipatory before the next dosing regimen)
- The most effective drugs:
    * 5-HT3 receptors antagonists: ondansetron
    * D2-dopamine antagonists: metoclopramide

  They may be used in combination with:
    * a benzodiazepine (anxiety is a major factor in promoting vomiting when the patient knows that it will occur as with cisplatin)
    * dexamethasone: unknown mechanism, probably by reducing edema around the vomiting centre.

Other drugs: prochlorperazine, domperidone, nabilone

Combinations are often more effective than a single drug e.g.

benzodiazepine plus dexamethasone plus: a 5-HT3 blocker (ondansetron) or D2- receptor blocker (metoclopramide)

Bone marrow suppression

- Is the single most important dose-limiting factor with cytotoxics
- Is associated with the twin danger of:

* **infection**: often oppportunistic by Gram-negative bacteria e.g. from the gut. Others: virus (H.zoster), fungus (candida), protozoa (pneumocystis).
* **bleeding**: due to thrombocytopenia

Bone marrow suppression could be:

- **deliberate** e.g. in treatment of leukemia
- **toxicity** which could be:
  * **rapid** e.g. nitrogen mustard, cyclophosphamide, MTX, vinblastine, ….
  * **delayed** e.g. nitrosureas (BCNU, CCNU), melphalan (for 6-12 weeks)

All cytotoxic drugs cause significant bone marrow suppression except bleomycin and vincristine. These two drugs cause no or minimal BM suppression

Alopecia (Reversible hair loss)

The most frequent offenders are: adriamycin and cyclo-phosphamide

Fertility

1. Females: do not usually have any long term effect on fertility although frequently stop menstruation

2. Males: profound reduction in sperm count particularly with alkylating agents
3. No conception should be attempted when one partner is being treated. The safe period is unknown, probably 4-6 months

Hyperuricemia

- May occur with lymphoma and leukemia
- Can be worsened by chemotherapy
- May cause acute renal failure
- Allopurinol can be started 24 hours before treating such tumors; patients should be well hydrated
- With allopurinol, the dose of mercaptopurine and azathioprine should be reduced

Endocrine Therapy

The growth of some tumours is hormone-dependent and may be inhibited by:

* administration of opposite hormones, hormone antagonist of estrogens, progestogens or androgens, or inhibitors of hormone synthesis

Examples

Tamoxifen: an estrogen-receptor antagonist. Used for breast cancer in post-menopausal women. In estrogen receptor +ve; response is 60%; in –ve response is only 10%.

Aminoglutethimide: inhibit conversion of androgens to estrogens (for breast cancer)

Gonadorelin analogues e.g. goserelin: After initial stimulation, inhibition of testosterone release occurs (for prostatic cancer)

Finasteride

An inhibitor of the enzyme 5α-reductase which activates testosterone (used in benign prostatic hypertrophy, BPH)

Adrenocorticosteroids

- Cytotoxic for cancers of lymphoid tissue and blood
- Also to treat some cancer complications such as hypercalcemia and raised intracranial pressure. It can have euphoric or mood-elevating effect and used in treatment of nausea and vomiting induced by cytotoxic drugs

Combination of anticancer therapy

- Drugs having different mechanisms of action in order to minimize drug resistance.
- Drugs with different spectra of clinical toxicity allowing administration of full doses of each drug

  Example

  MOPP for Hodgkin's lymphoma

  M = Mustine (nitrogen mustard)

  O = Oncovin (vincristine)

  P = Procarbazine

  P = Prednisolone

  5- FU combined with cyclophosphamide and MTX (CMF regimen) is used for treatment of many women with breast cancer

Biological Therapy

- Naturally occurring substances which regulate cell function can be used to treat cancer

  * Interleukins which stimulate proliferation of T-lymphocytes and activate natural killer cells.

  * Interferons and cytokines can also be used.

Immunotherapy

- Non-specific stimulation of active immunity with vaccines e.g. BCG instilled into the urinary bladder for bladder cancer.
- Passive immunotherapy with monoclonal antibodies raised against specific tumour-associated antigens

47. Immunopharmacology

Immunosuppressant drugs are useful in the following situations:

1. Suppress rejections in organ transplantation
2. Autoimmune disorders
3. Some collagen and connective tissue disease

The main group of drugs used in immunosuppression includes:

1. Ciclosporin and Tacrolimus
2. Mycophenolate Mofetil
3. Corticosteroids 4. Cytotoxic drugs: azathioprine, cyclophosphamide and chlorambucil
5. **Monoclonal antibodies: Basiliximab and daclizumab**
6. **Antilymphocytic** immunoglobulin

1. Ciclosporin:

It is a polypeptide obtained from a soil fungus, which has a potent immunosuppressant action.

Mechanisms of action:

a. decrease proliferation of T lymphocytes by inhibiting calcineurine phosphatase enzyme, which decrease the synthesis and release of cytokines (interleukins, interferon and tumor necrosis factor)
b. reduce the function of T cells
c. reduce the B cell responses which are dependent on T lymphocytes

It has little effect on phagocytic activity and does not cause bone marrow suppression

Pharmacokinetics:

Absorption from the GIT is variable with bioavailability ranging from 20% to 50%. It is widely distributed in the body, metabolized by the liver, and has a half-life of about 24 hours. Serum level monitoring is required

especially in renal transplantation to avoid toxicity and improve response to the drug

Adverse effects:

1. nephrotoxicity is the major adverse effect and related to the dose and serum level of the drug, it is probably due to vasoconstriction of the renal blood vessels.
2. Transient liver dysfunction
3. hypertension, and electrolytes disturbances (has mineralocorticoids activity)
4. hirsutism and acne (glucocorticoids activity)

Drug interactions with ciclosporin:

a. increased plasma levels and toxicity of ciclosporin by enzymes inhibitors as: ketoconazole, erythromycin and cimetidine
b. decrease in plasma level (reduce effect) by enzyme inducer drugs as:

phenytoin, carbamazepine, phenobarbitone and rifampicin

c. aggravation of renal damage by other nephrotoxic drugs as aminoglycosides and amphotericin

2. Tacrolimus:

Is a macrolide (polypeptide), structurally unrelated to ciclosporin, but has a similar mechanism of action. It is useful in renal and liver transplants.

side effects:

tends to cause more nephrotoxicity than ciclosporin more hirsutism, it also causes cardiomyopathy, hyperkalemia and significant disturbances of glucose metabolism.

3. Mycophenolate Mofetil:

Is a synthetic derivative of mycophenolic acid isolated from mold.

It inhibits T and B lymphocytes responses. It inhibits purine and nucleic acids synthesis. Mycophenolate Mofetil is hydrolyzed into mycophenolic acid, which is the active immunosuppressive molecule; however, the parent compound has better bioavailability.

Mycophenolate is used in solid organ transplantation usually in combination with prednisolone as an alternative to ciclospoprin or tacrolimus in patients who do not tolerate the drug. It is also used in lupus nephritis and rheumatoid arthritis.

Adverse effects:

a. Gastrointestinal disturbances (nausea, vomiting, diarrhea and abdominal pain)
b. Bone marrow suppression with neutropenia

4. **Corticosteroids**:

Corticosteroids are cytotoxic to T and B lymphocytes and can suppress both cellular and humeral immunity; they inhibit prostaglandins synthesis and transcription of cytokines. Corticosteroids also inhibit the phagocytic activity and reduce the rate of cellular destruction (as in autoimmune-hemolytic anaemia). In general, corticosteroids can reduce the lymph content of the lymph node.

Uses:

a. in organ transplantation, usually in combination with other immunosuppressant drugs
b. in autoimmune diseases include:

- Autoimmune hemolytic anaemia
- Idiopathic thrombocytopenic purpura
- Systemic lupus erythematosus
- Hashimoto thyroiditis

- Bronchial asthma

5. **Azathioprine**:

Is a derivative of 6-mercaptopurine, which is an antimetabolite cytotoxic drug acting by inhibiting cellular proliferation following antigenic stimulation. It can destroy stimulated lymphoid cells. It suppresses nucleic acid synthesis in the proliferating cells, so it inhibits cellular immunity as well as humeral immunity (antibody production by the plasma cells)

It is well absorbed from the gastrointestinal tract and converted first into mercaptopurine, which is the active metabolite, then mercaptopurine is inactivated by xanthine oxidase enzyme. The dose of the drug should be reduced in patient receiving allopurinol which is a xanthine oxidase inhibitor

Uses:

a. Renal transplantation
b. Acute glomerulonephritis
c. Renal component of systemic lupus erythematosus
d. Rheumatoid arthritis

Adverse effects:

a. bone marrow suppression with leucopenia, anaemia and thrombocytopenia
b. skin rash, fever, nausea, vomiting and diarrhea
c. hepatic dysfunction with elevation of liver enzymes and mild jaundice.

6. **Cyclophosphamide (**an alkylating agent**)**

It is one of the most effective immunosuppressant drugs available.

Cyclophosphamide destroys the proliferating lymphoid cells and in large doses it can affect the resting cells and can impair antigen recognition. In smaller doses, it is very effective against autoimmune disorders as systemic lupus erythematosus and autoimmune haemolytic anaemia.

Adverse effects:

a. bone marrow suppression with pancytopenia
b. haemorrhagic cystitis
c. nausea, vomiting, cardiotoxicity and electrolytes disturbances

7. Basiliximab and dacclizumab

Are monoclonal antibodies that inhibit T lymphocytes proliferation, they are used for the prophylaxis of acute allograft rejection in renal transplantation. They are given in combination with ciclosporin and corticosteroids

8. Antilymphocytic immunoglobulin (ALG):

Antilymphocytic immunoglobulins can be obtained by immunization of large animals such as horses or sheep with human lymphoid cells. ALG acts on peripheral lymphocytes with continuous use it affect the thymus dependent lymphocytes. As a result of inactivation of T lymphocytes, an impairment of delayed hypersensitivity and cellular immunity occurs, while humeral immunity remains intact. ALG are useful in organ and bone marrow transplantation and autoimmune disorders.

Adverse effects:

a. Anaphylactic and serum reaction to the immunoglobulin
b. Renal damage
c. May increase the risk of carcinoma

Hazards of immunosuppression therapy:

a. increase liability for infections, bacterial, viral or fungal

b. corticosteroids adverse effects
c. bone marrow suppression with azathioprine and cyclophosphamide

49. Toxicology: heavy metal poisoning

It is widely accepted that all substances are poisons if given in high doses. In therapeutic doses, they are considered remedy with some degrees of side effects.

Chemical with potential toxicity can reach various body tissues after absorption from the skin, absorption through GIT or through inhalation.

Toxic chemicals produce tissue damage through many mechanisms:

1. Some chemicals result in denaturation of macromolecules (proteins) which is essential for cellular functions.
2. Interference with enzymes such as an inhibitor to cholinesterase enzyme (malathion), or interference with normal body processes (warfarin) as rodenticide which inhibits vitamin K-dependent modification of clotting factors.

Heavy metal poisoning:

1. Lead
2. Mercury
3. Thallium poisoning

   Heavy metals exert their toxicity through binding to active functional groups on the macromolecules such as hydroxyl groups, carboxylic acid groups, sulfhydryl groups, and amino groups.

1. **Lead Poisoning**
   - is widely distributed in the environment
   - source of exposure from old paints, drinking water, food, contaminated dust

- from the GIT, 10% is absorbed in adults and more than 40% absorbed in children

Features of lead poisoning:

A. CNS

- lead encephalopathy: headache, fatigue, confusion, insomnia, impaired concentration.
- Blood concentration of (20 ug/dL) in children, lowers IQ

B. GIT system

Constipation

Abdomen colic

C. Blood

Hypochromic microcytic anemia

D. Cardiovascular system

Elevation of blood pressure

2. <u>Mercury poisoning</u>

- Exposure to mercury is due to contamination from industries.

Features of lead poisoning:

Organic mercury exposure

Organic or inorganic mercury poisoning usually results from ingestion of contaminated food. Onset of signs and symptoms of poisoning usually is delayed and appears days to weeks after exposure.

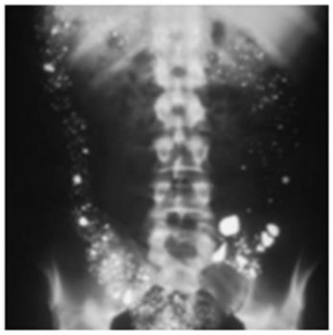
Organic mercury targets body enzymes, and the depletion of these enzymes occurs before the onset of symptoms.

Symptoms of mercury poisoning:

- Visual disturbance - Eg, scotomata, visual field constriction

- Tremors
- Depression
- Memory loss
- Inflammation of the kidneys
- Ataxia
- Paresthesias (early signs)
- Hearing loss
- Dysarthria
- Mental deterioration
- Muscle tremor
- Movement disorders
- Paralysis and death - With
- severe exposure

Abdomen X-Ray revealing mercury in intestine (taken from internet)



Treatment of acute poisoning: (Ref: P.N. Bennette and M.J. Brown, 2008; BG Katzung, 2007)

A. Activated charcoal: it can be described as a fine black powder prepared from woods, or coconut capsule. These materials are treated with high pressure stream of oxidizing gas to create small pores in order to increase the adsorbent surface area in these materials. It is safe but repeated doses may cause constipation and intestinal obstruction. Activated charcoal can bind to a large number of toxins but adsorption of some substances are not affected such as: (www.m.webmed.com)

1. Iron, lithium, alcohol
2. Cyanide
3. Strong acids and alkalis
4. Corrosive agents

B. Specific antidotes (chelating agents)

- Dimercaprol (2,3 dimercaptopropanol, BAL) (BAL = British anti-Lewisite) (available for IM only) acts by donating SH- groups to the metal ions to form relatively inactive compound which can be eliminated in urine.

  Adverse effect of dimercaprol: nausea, vomiting, lachrymation, salivation, paraesthesia, muscular pain, hypertension, pain at the site of I.M. injection and high doses may lead to convulsion and coma.
- Unithiol (DMPS, **D**i**m**ercaptopro**p**ane**s**ulphonate) (available in oral and i.v. dosage form): these compounds chelate inorganic mercury and lead. Side effect is less common than dimercaprol including dermatological reaction or hypotension following rapids infusion.
- Succimer (DMSA, **D**i**m**ercapto**s**uccinic **a**cid): it is water soluble form of dimercaprol. Used for lead or mercury. Side effects are: skin rash, elevation of liver enzymes and neutropenia
- Ethylendiaminetetraacetic acid (EDTA): used for Lead poisoning

3. Thallium poisoning

Thallium is a heavy metal which is discovered by Sir William Crookes in 1861. It is named from the Greek word “Thallos” (green twig).

Thallium is an extremely toxic heavy metal. It is colorless, odorless and tasteless, these features make thallium a substance which can be used in suicide or in deliberate poisoning.

in the past, before the introduction of antibiotics, thallium was used in medicine as a treatment for syphilis, gonorrhea, tuberculosis, ringworm and as depilatory for excess hair (hair removal). It has been still in use as rodenticide and ant killer in countries such as Russia and China.

Thallium is still in use in certain factories (Non-Medical uses) such as in optical lenses, photocells, semiconductor materials, gamma radiation detection equipments, imitation jewelry, artist’s paints, low temperature thermometers and green fireworks. In these factories workers are at risk of exposure to thallium.

Ways of exposure:

1. oral ingestion is the commonest way
2. it can be absorbed from skin
3. respiratory absorption

The lethal dose is approximately 15-20 mg/kg which is roughly one gram, 200 mg may cause severe poisoning.

History of thallium poisoning: these events are listed in chronological order

1934: 692 cases of poisoning were reported in the USA after the use of a compound “Koremlu” which was marketed for

treatment of ringworm and as depilatory agent (hair removal cream)

1993: 2 in the north of Iraq (BMJ, volume 306 5 June 1993)

1996-2008: 50 cases were reported in Russia

2006 : 20 victims in Russia

2008 :10 subjects in the Middle East (MMWR Morb Mortal Wkly Rep 2008 Sep 19; 57(37):1015-8

2009 : 2 in Prague (Hum Exp Toxicol 2009 28(5) 263-72

2012: One case report in a child 4.5 years old in Falluja, Al Anbar, western part of Iraq which, although no conclusive, is attributed to contamination of a river water nearby child's residency (Al Anbar Medical Journal, Volume (10), 2012, page 96-99, www.iasj.net/iasj?func=fulltext&ald=70913).

Signs and symptoms of thallium poisoning

Time 0 : exposure to thallium

3-6 h : gastrointestinal symptoms last for 12-96 h
nausea, vomiting, diarrhea (non-febrile)

2-5 d : painful rapidly progressives ascending
peripheral neuropathy. (last for weeks to
months) and optic nerve damage
cranial nerves dysfunction II, III, IV, VI
Distal motor weakness.
Ataxia, tremor, headache, seizures, coma.
pneumonitis, pulmonary oedema
acute myocardial injury.
renal damage (proteinuria, tubular necrosis)
Hepatic damage (jaundice)

7-12 d : alopecia is a hallmark of thallium poisoning
commonly involve the scalp
generally not permanent
complete hair loss occurs by one month
Alopecia and neuropathy may be the only presenting symptoms in case of chronic thallium poisoning.

30 d : Mees lines (horizontal white deposition in the nails).

Differential Diagnosis:

Guillain-Barre syndrome

Botulism

Heavy metal poisoning (arsenic, mercury, lead)

organophosphorous compound poisoning

Selenium poisoning

Carbon Monoxide poisoning

Diagnosis:

Atomic absorption photo spectrometry is used for determination of thallium level:

Urine: 24-h urine thallium concentration is the standard method.

Normal level= less than 5 mcg/l

Toxic level = 100-3000 mcg/l

Blood: Normal level= less than 2 mcg/l

Toxic level = 50-1400 mcg/l

Other parameters help in diagnosis and follow up :

Complete blood count, Serum electrolyte, abdomen X- ray because thallium is radio opaque, nerve conduction study, EEG, ECG, and

microscopic inspection of scalp hair: presence of dark black and brown pigment in the hair root in approximately 95% of cases

Treatment of thallium poisoning

1. Activated charcoal: repeated administration 0.25-0.5 g/kg every 2-4 h
2. Prussian Blue (Berlin Blue)
3. Hemodialysis as early as possible.

Forced diuresis is no longer advice

Chelating agents as EDTA, dimercaprol, D-pencillamine, BAL are not effective.

Prussian Blue (Berlin Blue)

Prussian Blue is “potassium ferric hexa-cyanoferrate”

it is a pigment discovered in 1700 and approved by the FDA in 2003 as an antidote for thallium poisoning

Mechanism of action:

Prussian Blue forms insoluble complex with thallium ions exchanging for potassium.

Prussian blue interferes with absorption of thallium from the Gut

Dose of Prussian Blue: 250 mg/kg/day (capsule) for 2 weeks?? or can be safely discontinued when urine thallium level < 100mcg/l

Side effects of Prussian Blue

constipation so you may add mannitol

50. Drugs and the skin

The main reference: Bennett et al (editors). Clinical pharmacology, Edinburgh …, Churchill Livingstone, Eleventh edition, 2012

Stratum corneum (superficial keratin layer) has two functions:

- It is the principal barrier to penetration of drugs
- It acts as a reservoir for drugs (a corticosteroid may be detectable even 4 weeks after a single application)

Drug absorption through the skin is determined by the:

- type of vehicle in which the drug is presented
- physicochemical properties of the drug (lipid-soluble vs water soluble)
- degree of hydration of stratum corneum (hydration increases diffusion)
- site of application: absorption is low in sole of foot and palm of hand
- state of skin: in damaged skin (as by inflammation, burn,..) absorption increases
- occlusive dressing can increase absorption by 10-folds (e.g. impermeable plastic membrane, plastic pants for babies)

Topically-used substances for skin diseases

1. Keratolytic agents: used to destroy unwanted tissue e.g. warts, corns. Examples: trichloroacetic acid and salicylic acid. Resorcinol and sulphur are mild keratolytic agents used in acne.
2. Dithranol (Anthraline) has anti-proliferative and anti-inflammatory effects on psoriatic and normal skin
3. Tars: are mildly antiseptic, antipruritic, and inhibit keratinization, used in psoriasis.
4. Zinc oxide: provides mild astringent, barrier and occlusive actions. Calamine; is a basic zinc carbonate; its pink color is due to added ferric oxide. It has a mild astringent action.

5. Psoralins (occurs naturally in some fruits and vegetables such as common fig, celery, …) e.g. methoxsalen; are used to induce photochemical reactions in the skin.

Topical or systemic administration of psoralens with subsequent exposure to ultra-violet light type A (UVA)(called PUVA therapy), results in an erythematous reaction; melonocytes are activated and pigmentation occurs over the following week; used to treat depigmenting conditions e.g. vitiligo.

In addition, in presence of UVA, psoralen interacts with DNA to inhibit its Synthesis, and, therefore, used in severe psoriasis.

Psoriasis

In psoriasis, there is increased epidermal proliferation (x10), inflammation of epidermis and dermis and increased number of cells containing abnormal keratin.

Drugs are used in treatment of psoriasis to:

a) dissolve keratin (keratolysis)

b) inhibit cell division

Drugs used in treatment of psoriasis include:

Emollient such as aqueous cream.

Elimination of proliferating cells e.g. dithranol (antimitotic).

Tar is an alternative to dithranol, but less effective.

Topical adrenal corticosteroids

Vitamin D derivatives e.g. calcipotriol (inhibits cell proliferation and encourage cell differentiation).

Vitamin A derivatives e.g. acitretin (inhibits psoriatic hyperkeratosis, it is teratogenic like other vitamin A derivatives)

UVB light

Psoralen followed by UV light (PUVA)

Ciclosporin

Folic acid antagonists e.g. methotrexate

Topical Adrenal Steroids in Psoriasis: Occlusive therapy can be very effective, but rebound may be severe following withdrawal

Systemic corticosteroids should be avoided in psoriasis because high doses are needed to suppress the disease, which is liable to recur in a more severe form when treatment is withdrawn.

Acne vulgaris

Acne vulgaris results from disordered function of pilosebaceous follicle where. Abnormal keratin and sebum form debris that plugs the mouth of the follicle (Sebum production is androgen dependent). The debris is colonized by bacteria (propionibacterium acnes). Bacterial action releases inflammatory fatty acids from the sebum resulting in inflammation

Treatment of acne

1. Mild keratolytic (peeling) agents to unblock pilosebaceous ducts e.g. benzoyl peroxide, sulfur, salicylic acid, azelaic acid
2. Systemic or topical antimicrobial drugs such as tetracyclines (e.g. doxycycline) and erythromycin (systemically) and clindamycin (topically). They are used over months. Benefit is due to suppression of bacterial lipolysis of sebum, thus, inhibiting the generation of inflammatory fatty acids.
3. Vitamin A (retinoic acid) derivatives reduce sebum production and keratinization

Tretinoin (Retin-A) is applied topically (but not with other keratolytics). It should be avoided in sunny weather and in

pregnancy. Benefit is seen in weeks. Isotretinoin orally is highly effective. But it is a serious teratogen. Women of child-bearing potential should be pregnancy tested before treatment and use contraception for 4 weeks before, during and for 4 weeks after cessation.

4. Hormone therapy to reduce androgen production or effect, by using: estrogen, antiandrogen (cyproterone), combination of estrogen and cyproterone.

Skin lightening agents

Hydroquinone

Hydroquinone is used to inhibit melanin production.

Topical hydroquinone comes in 2% to 4% (or more) alone or in combination with tretinoin 0.05% to 0.1%.

They are used to prevent sun- or hormone-induced melasma.

It can only disrupt the synthesis of melanin hyperpigmentation.

It has been banned in some countries (e.g. France) because of fears of a cancer risk.

Hydroquinone can be irritant, particularly in higher concentrations of 4% or greater and particularly when combined with tretinoin. A corticosteroid can be included with them as an antiinflammatory.

Antiseptics

Antiseptics are antimicrobial substances that are applied to living skin to reduce the possibility of infection

Disinfectants destroy microorganisms found on non-living objects

Examples of antiseptics

Alcohol, Benzalkonium (used e.g. in antiseptic towels), Boric acid (used e.g. in eyewashes), Chlorhexidine, Hydrogen peroxide, Iodine (Povidone-iodine), Phenolic compounds

Alcohols

The most commonly used is ethanol (60-90%). One use is to disinfect the skin before injections are given.

Chlorhexidine

is effective on both Gram-positive and Gram-negative bacteria.

The mechanism of action being membrane disruption.

Chlorhexidine is also useful against fungi and enveloped viruses.

Chlorhexidine is harmful in high concentrations, but is used safely in low concentrations in many products, such as mouthwash and contact lens solutions

Hydrogen peroxide

Used as a 6% solution to clean and deodorize wounds and ulcers. The strong oxidization may cause scar formation and delays healing. Gentle washing with mild soap and water or rinsing with sterile saline is a better practice.

Iodine

Tincture of iodine (alcoholic solution) and Lugol's iodine solution are no longer recommended to disinfect minor wounds because they induce scar tissue formation and delay healing.

Povidone-iodine (a complex of povidone, a water-soluble polymer, with triiodide anions, containing about 10% of active iodine) are better tolerated, don't negatively affect wound healing, and leave no persistent effect.

The great advantage of iodine antiseptics is their wide range of

antimicrobial activity, killing all principal pathogens and, if given enough time, kill even spores.

Phenol (carbolic acid) compounds

Phenol is germicidal in strong solution, germistatic in weaker solutions. They are used for pre-operative hand cleansing and in the form of a powder as an antiseptic baby powder. Also used in mouthwashes and throat lozenges, where it has a painkilling effect as well as an antiseptic one.

The End