Pharmacology

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Introduction to pharmacology

Introduction to Pharmacology

A. Definitions:

1. Pharmacology:- it defined as that science which deals with study of drugs and their action on the living organism.

2. Drug: - it is alchemical substance that has effect on living organism . Drugs are generally given for the diagnosis, prevention, control or cure of disease.

3. **Pharmacodynamics:** The study of the biological and therapeutic effects of drugs (i.e,"what the drug does to the body").

4. **Pharmacokinetics:** Study of the absorption, distribution metabolism and excretion (ADME) of drugs ("i.e what the body does to the drug").

5. **Chemotherapy:** It's the effect of drugs upon microorganisms, parasites and neoplastic cells living and multiplying in living organisms.

II. Pharmacodynamics : Involves how the drugs act on target cells to alter cellular function.

III. Pharmacokinetics: Pharmacokinetics deals with the absorption, distribution, metabolism and excretion drugs in the body.

1- Absorption :- it is process by which a drug is made available to the body fluids for distribution so drug transfer from site of entry to circulating fluid (blood, lymph)

Rate of absorption depends on

1:- route of administration:

2: blood flow

3:- solubility of drug

Notice/ Regardless of route of administration, the drug must be dissolved in body fluids before it can be absorbed in to body tissue

2- Distribution: - refer to the way in which drug are transported by the circulating body fluid to the sites of action (receptor)

It depend on :-

A- size of organ.

EX, skeletal muscle takes up large amount due it large organ

EX, brain takes small amount due it small organ

B**- blood flow**

*the most extensive blood supply like heart, liver, kidney & brain / rapid distribution

*the less extensive blood supply like muscle, skin, fat slowly distribution

C- solubility : lipid solubility

Ex. High lipid soluble drugs dissolved more rapidly in brain tissue than low lipid soluble due to the brain have high lipid.

D: - **binding:-** binding of drug to macromolecule in blood or tissue will increase drug concentration in blood or tissue

Examples

* Warfarin is strongly bound to balsam albumin

*Chloroquine is strongly bound to tissue protein

3- Metabolism: - the enzyme system of the liver is the primary site of the metabolism of drugs Other tissue and organs metabolism certain drug minor .Some drug metabolism before excretion example local anesthesia Other aren't metabolism like penicillin (G) they continue to act until they are excreted

4- Excretion of drugs

Excretion of drugs means the transportation of unaltered or altered form of drug out of the body. The major processes of excretion include renal excretion, hepatobiliary excretion and pulmonary excretion. The minor routes of excretion are saliva, sweat, tears, breast milk, vaginal fluid, nails and hair.

Different routes of drug excretion

a) **Renal excretion:** A major part of excretion of chemicals is metabolically unchanged or changed. The excretion of drug by the kidney involves.

i) Glomerular filtration

ii) Active tubular secretion

iii) Passive tubular reabsorption.

b) **Hepatobiliary excretion: e.g** Corticosteroids

c) **Gastrointestinal excretion:** The drugs which passed with stool e.g. aluminium hydroxide changes the stool into white colour, ferrous sulfate changes the stool into black and rifampicin into orange red.

d) **Pulmonary excretion:** Drugs that are readily vaporized, such as many inhalation anaesthetics and alcohols are excreted through lungs..

e) **Sweat**: A number of drugs are excreted into the sweat either by simple diffusion or active secretion e.g. rifampicin, metalloids like arsenic and other heavy metals.

f) **Mammary excretion:** Many drugs mostly weak basic drugs are accumulated into the milk. Therefore lactating mothers should be cautious about the intake of these drugs because they may enter into baby through breast milk and produce harmful effects in the baby e.g. ampicillin, aspirin, chlordiazepoxide, coffee, diazepam, furosemide, morphine, streptomycin

Bioavailability:

It is the rate and amount of drug that is absorbed from a given dosage form and reaches the systemic circulation following non-vascular administration. When the drug is given IV, the bioavailability is 100%.

Half life:

Half life (t1/2) of a drug: is the time taken for the concentration of drug in the blood or plasma to decline to half of original value or the amount of drug in the body to be reduced by 50%.

Drug interactions:

It is usual for patients to receive a number of drugs at the same time. It is a phenomenon which occurs when the effects of one drug are modified by the prior or concurrent administration of another drug(s).

Drug Synergism: When the therapeutic effect of two drugs are greater than the effect of individual drugs, it is said to be drug synergism.

Drug Antagonism: The phenomenon of opposing actions of two drugs on the same physiological system is called drug antagonism. Like Antagonism between acids and alkalis, Acetylcholine and atropine antagonism at muscarinic receptors, Acetyl choline causes constriction where as adrenaline causes dilatation of pupil.

Importance of drug antagonism

(i) Correcting adverse effects of drugs

(ii) Treating drug poisoning.

e.g. Morphine with naloxone, organophosphate compounds with atropine.

(iii) Predicting drug combinations which would reduce drug efficacy.

Drug tolerance:

When an unusually large dose of a drug is required to elicit an effect ordinarily produced by the normal therapeutic dose of the drug, the phenomenon is termed as drug tolerance.

Adverse drug reactions:

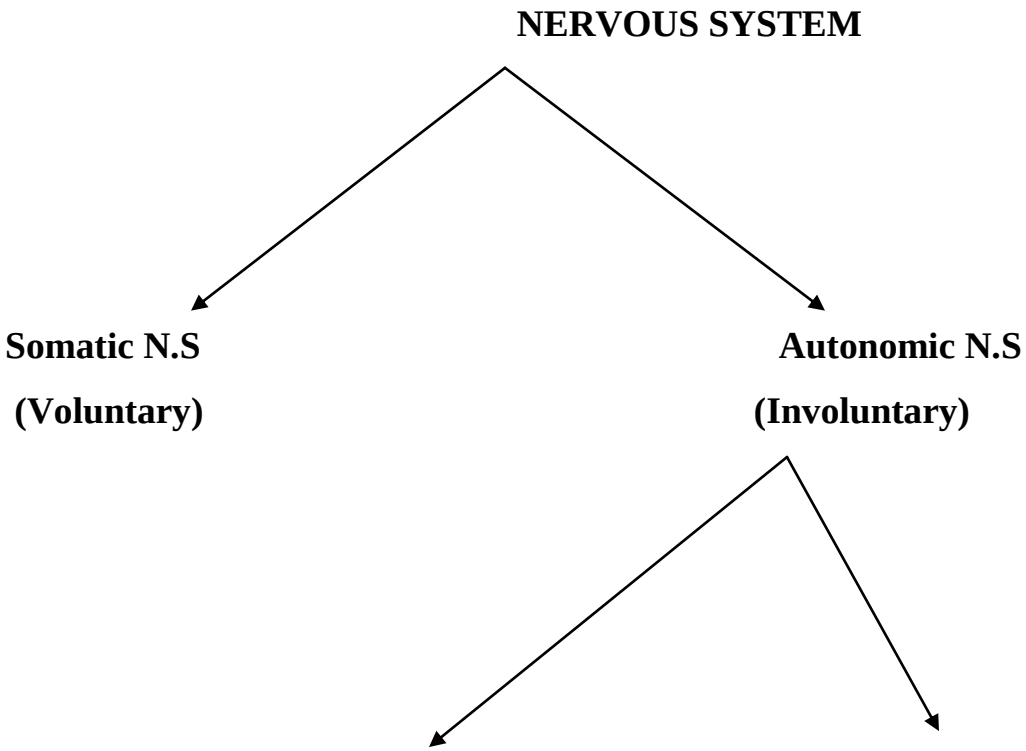
The drugs that produce useful therapeutic effect may also produce unwanted or toxic effects. e.g. Hypotension following antihypertensive drugs. Hypoglycaemia following insulin.

Teratogenic effect: Some drugs given in the first three months of pregnancy may cause congenital abnormalities and are said to be teratogenic. The drugs with teratogenic potential are androgens, steroids, anti convulsants, anti-neoplastic drugs, cortisone, lithium, pencillamine, tricyclic antidepressants and warfarin.

Factors effecting the drugs action:-

1. Age
2. Body weight (B.W)
3.Metabolic rate
4. Illness
5:-Psygological aspects
6-Tolerance
7:- dependence

Autonomic Nervous System



Sympathetic N.S	Parasympathetic N.S
Segments (Thoraco-lambar)	cranio- sacral

SPINAL ROOTS OF ORIGIN

1- SYMPATHETIC (SANS)

Pre- ganglionic fiber originate from

a- Thoracic (T1-T12) from the cord

b- Lumbar (L1-L5) from the cord.

2- PARASYMPATHETIC

Pre- ganglionic motor fiber originate from

a- Cranial nerve nuclei III, VII, IX and X

b- Sacral segments (S2-S5)

Autonomic N.S:-

- Control of involuntary movement like heart smooth muscle
- The autonomic NS regulates the main process
- The Autonomic nervous system consists of pre-ganglia and post ganglia nerves.
- pre-ganglia (from Central Nervous System to ganglia)
- post-ganglia (from ganglia to effector organ or target organ) .

❑ atuonomic nervous system (ANS) is divided into sympathetic and parasympathetic branches

❑ efferent fibers originate in nuclei in the CNS

Parasympathetic Nervous System

Acetylcholine:- it is neurotransmitter parasympathetic & cholinergic nerves it is action include

1 - Decrease H R &cardiac output

2 - Decrease blood pressure (injection of Ach causes vasodilatation & decrease blood pressure

3- Increase salivary secretion &stimulates intestinal secretion & motility.

4- Increase bronchial secretion.

5 - Eye → constriction of pupil

Acetylcholine receptors include

1• **Nicotinic receptor:-** located in autonomic ganglia, adrenal medulla and neuromuscular junction (NMJ)

2• **Muscarinic receptor**:-

• M1 located in the CNS

• M2 non-neuronal receptors located on smooth muscle, cardiac muscle and glandular epithelium

Anti-Cholinergic Drugs

1- Hyoscine (scopolamine)

2- Hyoscine butyl bromide

3- Atropine

Uses of anticholinergic drugs

1- action on CNS against rigidity and tremor Parkinson

2- antiemetic (**hyoscin**) 10mg as tablets, three types a day.

3- sedative action (**hyoscin**)

4- dilate pupil (**Atropine**)

5- bronchodilator (**Ipratropine**)

Sympathetic Nervous System (SNS)

❑ norepinephrine is the major neurostransmitter of the SNS

❑ receptors include

• ß1 predominately in cardiac tissue

• ß2 predominately in smooth muscle and glands

❑ each receptor has a different sensitivity to sympathomimetics

Sympathomimetics

They drugs the mimic the effects of stimulation of the sympathetic division of the autonomic nervous system.

The includes substance which occur naturally in the body.

1- **Adrenaline**

2- **Nor adrenaline**

Notices:

1:- chlonergic fiber -- release Acetyl choline (Ach)

2:- adrenergic fiber – release adrenaline & noradrenalin

Neurotransmitter of A.N.S

1-ACH

2-norepineohrine

3 -serotonin

4- dopamine

5- histamine

Features of Neurotransmitter of A.N.S

1. Synthesis
2. Storage
3. Release
4. Termination of action

Some of Anticholinergic drugs are:

1-Atropine :

it belladonna alkaloid, Atropine is both a central & peripheral muscarinic blockers.

a- decrease salivary& bronchial secretion

b- In c.n.s IN PARKINSON DISEASE

c- Locally in eye→ dilation of the eye pupil so use in examination of retina

d- Analgesic

e- Antidote

f- before anesthesia to decrease bronchial secretions.

Sid effect of Atropine: Mouth dryness & increase pulse &constipation *Not used in glaucoma &heart failure

2- Scopolamine: (buscopan) ® an anticholinergic drug is very effective in reliving nausea & vomiting associated with motion sickness. Act on CNS. Used in motion sickness before anesthesia

3- Clidinum Librax® Ibraxam®

Uses: stomach infection, ulcer

4- B enzhexol Artane®

Uses in Parkinson disease

2- Adrenergic drugs (agonists):- Adrenergic drugs have many uses are:

1. Increase the output of the heart, to raise blood pressure.
2. Increase urine flow as part of the treatment of shock.
3. Heart stimulants. They may be given to a patient to reverse the drop in blood pressure that is sometimes caused by general anesthesia.
4. They may be used to stop bleeding by causing the blood vessels to constrict,
5. Local anesthetics .
6. Reduce nasal stuffiness associated with colds and allergies.
7. to open the bronchi (the tubes leading to the lungs) for treatment of asthma and chronic obstructive pulmonary disease (COPD).

Adrenergic drugs

Direct	Indirect	mixing
Dopamine	**Amphetamine**	**ephedrine**
Epinephrine	**-**	**-**

1- **Dopamine:** - used in shock stimulate beta-receptor in heart

2- **Dobuttamine:-**used in C.H.F so increase cardiac output

3- **Terbutalin and salbutamol (**bronchodilator)

4- **Amphetamine:-** is C.N.S stimulant, used in treatment of depression & appetite control

Side effect of the above drugs addiction lead to hypertension

5- **Ephedrine :** Actions of Ephedrine

1. Increase systolic &diastolic blood pressure
2. Pruduce bronchodilator
3. Mild stimulation of C.N.S
4. Treat of asthma & nasal decongestant

Drugs Affecting Respiratory System

INTRODUCTION

The respiratory system includes the upper airway passages, the nasal cavities, pharynx and trachea, bronchi, bronchioles lungs and alveoli. Respiration is the exchange of gases between the tissue of the body and to outside environment. It involves breathing in of an air through the respiratory tract, uptake of oxygen from the lungs, transport of oxygen through the body in the blood stream, utilization of oxygen in the metabolic activities and removal of carbon dioxide from the body.

Diseases of Respiratory System

- Upper respiratory tract: colds, rhinitis, hay fever

- Lower respiratory tract: asthma, emphysema and chronic bronchitis All involve obstruction of airflow through the airways.

Bronchial asthma

Asthma is physiologically characterized by increased responsiveness of the trachea and bronchi to various stimuli and by wide spread narrowing of the airways that change in severity either spontaneously or as a result of therapy Impairment of airflow in bronchial asthma is caused by three bronchial abnormalities.

i. **Contraction** of airway smooth muscles

ii. **Thickening** of bronchial mucosa from edema and cellular infiltration

iii. **Inspissations** in the airway lumen of abnormally thick, viscid plugs of excessive mucus.

Pharmacotherapy of Bronchial Asthma.

Drug used in the treatment of bronchial asthma can be grouped into three main categories:

1. Bronchodilators

a. β- Adrenergic agonists which include:

1. Adrenaline
2. Salbutamol

b. Methylxanthines e.g. **Theophylline derivatives**

c. Muscranic receptor antagonists e.g. **Ipratropium bromide**

2. Mast cell stabilizers, e.g. **Ketotifen**

3. Antiinflammatory agents: Corticosteroids

1. β- **ADRENERGIC AGONISTS (SYMPATHOMIMETIC AGENTS)**

a) Non- selective- β-agonist e.g. **Ephedrine**

b). Selective β-agonists **e.g. Salbutamol, Terbutaline**

Mechanism of Action

1. Relax smooth muscles
2. Inhibit release of broncho constricting substances from mast cells.
3. Inhibit microvasculature leakage
4. Increase mucociliary transport

Contraindication: - hypertension, arrhythmia,

Selective β2- selective agonists

Commonly used drugs both by oral and inhalation are **Salbutamol, Terbutaline,**

Duration of action 12 hrs or more. These drugs appear to interact with inhaled corticosteroids to improve asthma control.

Side effects : Tremors, anxiety, insomnia, tachycardia, headache, hypertension and etc.

Contraindications: hypersensitivity to the drug , hypertension, cardiac dysfunction, hyperthyroidism, glaucoma, diabetes, pregnancy.

2. Methylxanthines

- The three important methylxanthines are **Theophylline** and **Caffeine**. The theophylline preparations most commonly used for therapeutic purposes is Aminophylline

Adverse Effects: Anorexia, nausea vomiting, abdominal discomfort, headache, anxiety, insomnia, seizures, arrhythmias.

3. Muscarnic receptor antagonist

Mechanism of Action : block the contraction of air way smooth muscle.

Systemic adverse effects urinary retention, tachycardia.

4. Anti- Inflammatory agents:

Corticosteroids : Used for both treatment and prophylactic purposes

Effects on airway

1. Decreases bronchial reactivity
2. Increases airway caliber
3. Decreases frequency of asthma exacerbation and severity of symptoms

The corticosteroids commonly used are

1. Hydrocortisone
2. Predinisolone
3. Beclomethasone
4. Triamcinolone and etc.

These above drugs can be taken by inhalation as aerosol, oral, or an IV administration. Because of severe adverse effects when given chronically. Aerosol treatment is the most effective way to decrease the systemic adverse effect of corticosteroid therapy.

Side effects of Corticosteroids

1. Osteoporosis
2. Sodium retention and hypertension
3. Cataract
4. Impairment of growth in children
5. Susceptibility to infection like oral candidiasis, tuberculosis

Treatment of Status Asthmatics includes:

1 - Administration of oxygen

2 - Frequent or continuous administration of aerosolized ß2 agonists like **Salbutamol**

3 - Systemic corticosteroid like methyl **prednisolone** or **hydrocortisone** by IV injection.

4 - Aminophylline through **IV infusion**

5 - Iv fluid to avoid dehydration

6 - Antibiotics in the presence of evidence of infection

Treatment of cough

1. ## Anti-Tussives:

- **Cough** is a protective reflex, which serves the purpose of expelling sputum and other irritant materials from the respiratory airway.

Types of cough:

1. Useful productive cough
2. Cough Effectively expels secretions and exudates
3. Useless cough

- Non-productive chronic cough
- Due to smoking and local irritants

Anti-tussives : are drugs used to suppress the intensity and frequency of coughing. There are two **Types** of Anti-tussives:

1. Central anti- tussives: Suppress the medullay cough center and may be divided into two groups:

1. **Opoid antitussive** e.g. Codeine, Hydrocodeine, etc
2. **Non opoid antitussives** e.g. Dextromethorphan (Sedilar)

2. Peripheral antitussives: Decrease the input of stimuli from the cough receptor in the respiratory passage. **e.g: Cough Demulcents e.g. honey**

1. **Codeine:** Codeine is a narcotic relatively less addicting drug and central antitussive agent and it's main side effects are dryness of mouth, constipation and dependence.

2. **Dextromethrophan:** Dextromethorphan is an opoid synthetic antitussive, essentially free of analgesic and addictive properties and the main side effects are respiratory depression

2. Expectorants: is a drug that aid in removing thick tenacious mucus from respiratory passages, e.g. **Ipecac alkaloid, sodium citrate, saline expectorant, guanfenesin, potassium salts**

3. Mucolytics: are agents that liquefy the mucous.

Nasal Decongestants

Decongestants are the drugs that reduce congestion of nasal passages, which in turn open clogged nasal passages and enhances drainages of the sinuses.

e.g **phenylephrine, oxymetazoline etc.**

Mechanism of Action of nasal decongestion:

Produce localized vasoconstriction on the small blood vessels of the nasal membrane.

Clinical uses:

Used in congestion associated with rhinitis, hay fever, allergic rhinitis and to a lesser extent of common cold. These Drugs can be administered nasally or orally for longer duration of action.

Classification of decongestants:

1. Short acting decongestants administered topically e.g. **Phenylepherne**
2. Long acting decongestants administered orally e.g. **Ephedrine, Pseudoephedrine, Naphazoline**
3. Long acting topical decongestants e.g. **Xylometazoline & oxymetazoline**

Side effects:

1. Rebound nasal congestion

2. Nasal burning, stinging, dryness

3. Tachycardia, arrhythmia, nervousness, restlessness & blurred vision

Contraindications : Hypertension, severe coronary artery disease

Drugs used in Gastro-intestinal diseases

INTRODUCTION

The pharmacologically treatable disorders of impairments of normal motility, digestion, absorption, secretions of the gastrointestinal tract include peptic ulcer, reflux esophagitis, Zollinger-Ellison syndrome, constipation, diarrhea, inflammatory diseases and infections.

I. Drugs used in peptic ulcer disease:

Acid-peptic disease includes peptic ulcer (gastric and duodenal), gastroesophageal reflux and Zollinger – Ellison syndrome.

Peptic – ulcer disease is result from an imbalance between cell destructive effects of hydrochloric acid and pepsin. A bacterium, **Helicobacter pylori** is now accepted to be involved in the pathogenesis of ulcer.

Gastroesophageal reflux, acidic stomach contents enter into the esophagus causing a burning sensation in the region of the heart; hence the common name heartburn, or other names such as indigestion, dyspepsia etc.

Zollinger-Ellison syndrome is caused a tumor of **gastrin secreting cells** of pancreas characterized by excessive secretion of gastrin that stimulates gastric acid secretion.

Anti- Ulcer drugs

drugs used in the prevention and treatment of peptic ulcer disease act mainly to decrease cell-destructive effects.

A: Gastric acid neutralizers (antacids)

Antacids:

- Are alkaline substances (weak bases) that neutralize gastric acid (hydrochloric acid)
- They react with hydrochloric acid in the stomach to produce neutral or less acidic or poorly absorbed salts and raise the PH of stomach secretion.

Antacids are divided into systemic and nonsystemic

1. **Systemic,** e.g. sodium bicarbonate are absorbed into body fluids and may alter acid – base balance. It can be used in the treatment of metabolic acidosis.
2. **Non systemic,** do not alter acid – base balance significantly. They are used as gastric antacids; and include aluminium, magnesium and calcium compounds

• **Magnesium compounds** have a relatively high neutralizing capacity, rapid onset of action, cause **diarrhoea and hypermagnesemia**.

• **Aluminium compounds** generally have a low neutralizing capacity, slow onset of action but long duration of action and may cause **constipation**.

• **Calcium compounds** are effective and have a rapid onset of action but may cause hypersecretion of acid (acid - rebound) and milk-alkali syndrome (hence rarely used in peptic ulcer disease).

The most commonly used antacids, are mixtures of aluminium hydroxide and magnesium hydroxide **(e.g. Gelusil, Maalox etc).**

Gastric acid secretion inhibitors (antisecretory drugs):

HCl is secreted by parietal cells of the gastric mucosa which contain receptors for acetylcholine, histamine and gastrin that stimulate the secretion.

Antagonists of **acetylcholine**, **histamine** and **gastrin** inhibit acid secretion.

Antisecretory drugs include:

- **H2-receptors blocking agents** such as **cimetidine 200MG , ranitidine 150MG**
- **Proton pump inhibitors such** as**, Omeprazole**, **Lansoprazole, etc.** which is the common terminal step to release hydrogen ion into the gastric lumen.

Cytoprotective (mucosal protective) agents.

- Locally active agents help to heal gastric and duodenal ulcers by forming a protective barrier between the **ulcers** and **gastric acid, pepsin,** and **bile salts**.
- They do not alter the secretion of gastric acid. These drugs include **sucralfate** and **colloid bismuth compounds**. (e.g. tripotassium, dicitratobismuthate)

Laxatives and cathartics (purgatives)

Laxatives and **cathartics** are drugs used orally to evacuate the bowels or to promote bowel elimination (defecation).

Example:- **Castor oil**

Types of Laxatives

1. **Bulk forming laxatives:** are substances that are largely unabsorbed from the intestine. They include hydrophilic colloids such as **methylcellulose**. When water is added, the substances swell and become gel-like which increases the bulk of the fecal mass that stimulates peristalsis and defecation.

2. **Osmotic laxatives** such as **magnesium sulfate**, **magnesium hydroxide**, **sodium phosphate**, etc. also belong to bulk forming laxatives. These substances are not efficiently absorbed, thus creating a stronger than usual solution in the colon which causes water to be retained. The increase in pressure and volume causes stimulation of peristalsis.

3. **Stimulant (irritant) laxatives** (cathartics): are substances that are themselves irritant or contain an irritant substance to produce purgation. Individual drugs are castor oil, **bisacodyl, glycerine**, etc.
4. **Lubricant laxatives:** e.g. **liquid paraffin** (mineral oil).It lubricates the intestine and is thought to soften stool by retarding colonic absorption of fecal water.
   Used as retention enema.

5-Fecal softners: Decrease the surface tension of the fecal mass to allow water to penetrate into the stool. They have detergent – like property e.g. **Docusate**. They may also decrease water absorption through intestinal wall.

Indications for use Laxatives and cathartics are used to:

1. To relieve constipation – bulk forming
2. To prevent straining – stool softeners
3. To empty the bowel in preparation for bowel surgery or diagnostic procedures (saline or stimulant)
4. To accelerate elimination of potentially toxic substances from the GI tract (saline or stimulant)
5. To accelerate excretion of parasite after anthelmintic drugs (saline or stimulant) have been administered.

Constipation is a common problem in older adults and laxatives are often used or overused.

Non drug measures to prevent constipation (e.g. **increasing intake of fluid** and **high – fiber foods, exercise**) are much **preferred to laxatives**.

III. Antidiarrhoeals:

• Are used in the treatment of diarrhea, defined as the *frequent expulsion* of liquid or semi liquid stools → hinders absorption of fluids and electrolytes.

• Antidiarrheal drugs may be given to relive the symptom (non-specific therapy) or may be given to treat the underlying cause of the symptom (specific therapy).

• **Morphine** is effective but not used because of serious potential adverse effects, other synthetic drugs such as **diphenoxylate & loperamide** are commonly used

• Adsorbent – demulcent products such as **kaolin – pectin** preparations may be included in antidiarrheal preparations, unfortunately.

• Anticholinergic agents e.g. **Atropine** are occasionally used to decrease abdominal cramping and pain associated with diarrhea.

• Specific therapy may include the use of **antibacterial**, which are recommended for use in carefully selected cases of bacterial enteritis.

• Severe diarrhea by **salmonella, shigella, campylobacter and clostridia**. Species can be treated by antibiotics (ampicillin, chloramphinicol, colistin, co-trimoxazole
etc.

• Parasitic infections (giardiasis & ameobiasis can be treated by **(Metrandazol)**

Indications for use

1. severe or prolonged diarrhea (>2-3 days)
2. when specifice causes have been determined

Glucose – electrolyte solution should be given in severe cases for electrolyte and fluid replacement. It contains:

Glucose 20 gm

NaCl 3.5gm

NaHCO3 2.5gm

KCl 1.5gm

Add water to 1000ml

IV. Antiemetics:

• Are drugs used to prevent or treat nausea and vomiting.

Nausea is an unpleasant sensation of abdominal discomfort accompanied by a desire to vomit.

Vomiting is the expulsion of stomach contents through the mouth. Nausea may occur without vomiting and vomiting may occur without prior nausea, but the two symptoms most often occur together.

Vomiting occurs when the vomiting center in the medulla oblongata is stimulated.

- **Dopamine & Acetylcholine** play a major role in stimulating the vomiting center in the brain.
- **Antiemetic drugs** are generally more effective in prophylaxis than treatment.

Antiemetic drugs include:

1. Phenothiazines such as chlorpromazine
   - Acts on vomiting center in the brain.
   - Block dopamine receptors
   - Are effective in prevention or treating nausea and vomiting induced by drugs, radiation therapy, surgery and most other stimuli (e.g. pregnancy).

2. **Antihistamines** – such as promothazine, dimehydrinate etc . Are especially effective in prevention and treatment of motion sickness, but they may cause concurrent drowsiness.

Miscellaneous antiemetics

Metoclopramide (Plasil) has both central and peripheral antiemetic effects. Centrally, metoclopoamide antagonizes the action of dopamine. Peripherally metoclopoamide stimulates the release of acetylcholine, which in turn, increases the rate of gastric emptying (used in esophapeal reflux)

V. Drugs used to induce vomiting (Emetic drugs)

In case of poisoning with noncorrosive agents, and assuming incomplete absorption of the poison has taken place, induction of vomiting can be carried out. The drug used for this purpose is **Emetine**, the active ingredient of ipecacuanha (syrup of ipecac).

Emetine induces by direct irritation of the upper gut and on absorption.

VI. Drugs used in the treatment of haemorrhoids

Haemorrhoids are varicose veins of the anal canal which can be very distressing for the sufferer. There is no pharmacological cure for this disorder, which is often self-limiting, if not, may require surgical intervention.

The purpose of drugs usage:

1. Stool softeners may alleviate constipation; lessen straining which can worsen the condition.
2. Local anesthetics (e.g. lignocaine, benzocaine) relieve pain
3. Corticosteroids (e.g. predniosolone) suppress inflammation, itching & swelling
4. Vasoconstrictors (e.g. adrenaline, phenylephine) lessen venous swelling

5. Astringent compounds (e.g. tannic acid) reduce swelling by precipitating cell surface. Antihaemmorhoidal preparations contain one or more of these agents.

VII. Drugs used in inflammatory bowel disease (ulcerative colitis and crohn's disease)

• Ulcerative colitis is an inflammatory condition of the rectum and colon; crohn's disease can involve the whole intestine.

• Both diseases can lead to pain and ***abdominal discomfort***. Two groups of drugs used to treat both conditions are

1. corticosteroids e.g. **prednisolone**

2. drugs related to **sulphonamides e.g. sulfasalazine.**

Cardiovascular & Renal pharmacology

INTRODUCTION

In the past decades, cardiovascular diseases were considered as major health problems mainly for western countries. However, the problem of cardiovascular disorders is also increasing in developing countries . The most commonly encountered cardiovascular disorders include hypertension, congestive heart failure, angina pectoris and cardiac

arrhythmias. Most drugs available currently are able to reduce the morbidity and mortality due to these disorders, and therefore, this chapter discusses the pharmacology of these drugs.

I. Antihypertensive drugs

a. General consideration:-

Hypertension is defined as an elevation of arterial blood pressure above an arbitrarily defined normal value. The American Heart Association defines hypertension as arterial blood pressure higher than 140/90mmHg (based on three measurements at different times). **Hypertension** may be classified in to three categories, according to the level of diastolic blood pressure:

- **Mild hypertension** with a diastolic blood pressure between 95-105 mmHg
- **Moderate hypertension** with a diastolic blood pressure between 105 – 115mmHg
- **Severe hypertension** with a diastolic blood pressure above 115mmHg.

b. Antihypertensive therapies.

Anti - hypertensive drugs are classified according to the principal regulatory site or mechanism on which they act. They include:

A) Diuretics, which lower blood pressure by depleting the body sodium and reducing blood volume. Diuretics are effective in lowering blood pressure by 10 – 15 mmHg in most patients. **Diuretics include:**

a) Thiazides and related drugs, e.g. **Hydrochlorthiazide**. Initially, thiazide diuretics reduce blood pressure by reducing blood volume and cardiac out put

b) Loop diuretics, e.g**. Furosemide (Lasix).** Loop diuretics are more potent than thiazides as diuretics. The antihypertensive effect is mainly due to reduction of blood volume.

Loop diuretics are indicated in cases of severe hypertension which is associated with renal failure, heart failure or liver cirrhosis.

c) Potassium sparing diuretics, e.g. **Spironolactone**

They are used as adjuncts with thiazides or loop diuretics to avoid excessive potassium depletion and to enhance the natriuretic effect of others. The diuretic action of these drugs is weak when administered alone.

B) Sympathoplegic agents (Depressants of sympathetic activity)

Methyldopa

Is useful in the treatment mild to moderately severe hypertension.

The side effects of methyldopa include sedation, vertigo, dry mouth, nausea, vomiting, diarrhea, postural hypotension, haemolytic anemia.

C) Adrenoceptor antagonists, e.g **Propranolol** (beta blocker), **Prazosin** (alpha blocker), **Labetalol** (alpha and beta blocker).

forms of hypertension.

D) Direct vasodilators. These include:-

1. Arterial vasodilators, e.g. **Hydralazine**
2. Arteriovenous vasodilators, e.g. **Sodium nitroprusside**

The most common adverse effects are headache, nausea, anorexia, palpitations, sweating and flushing which are typical to vasodilators.

D) Angiotensin converting enzyme inhibitors, e.g. **Captopril, Enalapril**, etc. They inhibits angiotensin converting enzyme, which additionally stimulates the secretion of aldosterone. It lowers blood pressure principally by decreasing peripheral vascular resistance.

The adverse effects include maculopapular rash, cough and diminished taste sensation.

E) Calcium channel blockers, e.g. **Nifedipine, Verapamil**, etc. The mechanism of action in hypertension is inhibition of calcium influx in to arterial smooth muscle cells, resulting in a decrease in peripheral resistance.

The most important **toxic effects** for calcium channel blockers are cardiac arrest, bradycardia, atrioventricular block and congestive *heart failure.*

II. Drug used in heart failure

Congestive heart failure occurs when there is an inability of the heart to maintain a cardiac output sufficient to meet the requirements of the metabolizing tissues.

Heart failure is usually caused by one of the following:

- Ischaemic heart disease
- Hypertension
- Heart muscle disorders
- Valvular heart disease.

1. Cardiac glycosides.

Cardiac glycosides comprise a group of steroid compounds that can increase cardiac output and alter the electrical functions. Commonly used cardiac glycosides are **Digoxin** and **Digitoxin**.

Therapeutic uses of cardiac glycosides include:

1. Congestive heart failure
2. Atrial fibrillation,
3. Atrial flutter, and
4. Paroxysmal atrial tachycardia.

Toxicity of cardiac glycosides include:

1. Gastrointestinal effects such as anorexia, nausea, vomiting, diarrhoea
2. Cardiac effects such as bradycardia, heart block, arrhythmias
3. CNS effects such as headache, malaise, hallucinations, delirium, visual disturbances (yellow vision)

III) Pharmacotherapy of Angina pectoris

Angina pectoris develops as a result of an imbalance between the oxygen supply and the oxygen demand of the myocardium. It is a symptom of myocardial ischemia. When the increase in coronary blood flow is unable to match the increased oxygen demand, angina develops. It has become apparent that spasm of the coronary arteries is important in the production of angina.

Drugs used in angina pectoris

1. Organic nitrates e.g. **Nitro-glycerine, Isosorbide** etc.
2. Beta adrenergic blocking agents **e.g. propranolol, atenolol, etc.**

3. Calcium channel blocking agents **e.g. verapamil, nifedipine, etc.**
4. Miscellaneous drugs **e.g. aspirin, heparin.**

V) Pharmacotherapy of cardiac arrhythmias

Antiarrhythmic drugs are used to prevent or correct cardiac arrhythmias (tachyarrhythmias).

Drugs used in the treatment of cardiac arrhythmias are traditionally classified into:

Class (I): Sodium channel blockers which include Lidocain , etc.

Class (II): Beta adrenergic blockers which include Propranolol, Atenolol, etc.

Class (III): Potassium channel blockers e.g. **Amiodarone.**

Class (IV): Calcium channel blockers e.g. **Verapamil**, etc.

Class (V): Digitalis e.g. **Digoxin.**

VII. Drugs used in hypotensive states and shock

are used to elevate a low blood pressure and may be classified as follows:

I. ***Agents intended to increase the volume of blood in active circulation***. These include intravenous fluids such as whole blood, plasma, plasma components, plasma substitutes and solution of crystalloids

II. ***Vasoconstrictor drugs*** these include: Peripherally acting vasoconstrictors like **Noradrenaline** and **Ephedrine.**

Antibiotics

Antibiotics*:* are substances produced by various species of microorganisms (bacteria,fungi, actinomycetes) that suppress the growth of other microorganisms. we have two types of Antibiotics according to their action……..

1. **Bacteriostatic antibiotics**
2. **Bacteriocidal antibiotics**

Classification according to their mechanism of action:

1 • Cell wall synthesis inhibitors

– **Beta-lactams** (penicillins, cephalosporins, aztreonam, imipenem)

– **Poly-peptides** (bacitracin, vancomycin)

2 • Protein synthesis inhibitors

– Aminoglycosides

– Tetracycline

– Chloramphenicol

– Clindamycin

3 • Folate antagonists

– Sulfonamides

– Trimethoprim

4 • **Nucleic acid inhibitors ;** DNA inhibitor (Mitomycin) , RNA inhibitor (Rifampicin).

5 **.Cell membarane inhibitors** (polymyxin)

Principle of Antibiotics: Inhibit growth of bacteria without harming the host.

Resistance: loss of efficacy of a given AB against a particular strain.

Pencillin- Antibiotics

Selective Penicillins

1. Benzyl penicillin (penicillin V)

- Naturally occurring
- Poor oral availability (sensitive to stomach acid)
- Its half-life = 30 minutes
- Uses for Rx of acute tonsillitis, endocarditis
- given by injection (IM), in the form o vial.
- Active against gram-positive bacteria

2. Procain penicillin or penicillin G:

it has properties same as of that Benzyl penicillin, except it has longer time for action, which continue for many days, given parentally (IM inj.) in the dose of 400.000 iu, 600.000 iu or 800.000 iu.

3. **Benzathine penicillin (BP):** it's action continue for many weeks, in the form of vail (600.000 iu or 1200.000 iu)
4. **Ampicillin (** Broad spectrum antibiotic**)**
   - Good oral availability

- Active against gram-positive especially staphylococcus and gram negative bacteria like Neisseria.
- Active against enterobacteria
- Given orally or parentally (capsules 250 mg or 500 mg) or vails 500 mg.
- Indications include: bronchitis, otitis media, tonsillitis, laryngitis ….etc.)

5. Amoxicillin (Broad spectrum antibiotic)

- Excellent oral availability
- Given orally or parentally (capsules 250 mg or 500 mg) or vails 500 mg or 1000 mg.
- Indications include: respiratory indections (bronchitis and pneumonia), ear infections (otitis media), urinary infections (cystitis), gynecological infections, intra-abdominal infections, skin and soft tissue infections, typhoid and paratyphoid, joint infections and prevention of septicemia.

Cephalosporins- Antibiotics

Cephalosporins can be classified into four generations depending mainly on the spectrum of antimicrobial activity. First-generation compounds have better activity against gram-positive organisms and the later compounds exhibit improved activity against gram-negative aerobic organisms.

First generation cephalosporins

First generation cephalosporins are moderate spectrum agents. They are effective alternatives for treating staphylococcal and streptococcal infections and therefore are alternatives for skin and soft-tissue infections, as well as for streptococcal pharyngitis.

The first generation cephalosporins are:

1. Cephalexin
2. Cephalothin
3. Cefazolin

Second generation

The second generation cephalosporins have a greater gram-negative spectrum while retaining some activity against gram-positive bacteria. They are also more resistant to beta-lactamase. They are useful agents for treating upper and lower respiratory tract infections, sinusitis and otitis media. These agents are also active against E. coli, Klebsiella and Proteus, which makes them potential alternatives for treating urinary tract infections caused by these organisms.

The second generation cephalosporins are:

1. Cefoxitin
2. Cefuroxime

Third generation

Third generation cephalosporins have a broad spectrum of activity and further increased activity against gram-negative organisms. The parenteral third generation cephalosporins

(ceftriaxone and cefotaxime) have excellent activity against most strains of Streptococcus pneumoniae, including the vast majority of those with intermediate and high level resistance to penicillin. These agents also have activity against N. gonorrhea .

The third generation cephalosporins are:

1. Cefixime
2. Ceftriaxone
3. Cefotaxime

Fourth generation

Fourth generation cephalosporins are extended spectrum agents with similar activity against gram-positive organisms as first generation cephalosporins. They also have a greater resistance to beta-lactamases than the third generation cephalosporins. Many can cross blood brain barrier and are effective in meningitis.

Cefepime has broad gram-negative coverage with somewhat enhanced activity against pseudomonas but slightly lesser activity against pneumococci. **Cefepime** and **cefpirome** are highly active against nosocomial pathogens such as Enterobacter and Acinetobacter and their use should therefore be restricted to the setting of nosocomial sepsis.

The fourth generation cephalosporins are:

1. Cefepime
2. Cefpirome

Aminoglycosides- Antibiotics

Members: Streptomycin, Neomycin, Kanamycin, Amikacin, Gentamicin and others. Aminoglycosides are absorbed very poorly from the gastrointestinal tract. After intramuscular injection or intravenous injection, aminoglycosides are well absorbed.

Adverse effects: Aminoglycosides damage the **VIII nerve** and the kidneys. Ototoxicity, tinnitus and high-frequency hearing loss

Aminoglycosides including

1. ***Streptomycin:*** Streptomycin is mainly used as a first-line agent for treatment of tuberculosis & Brucellosis .
2. ***Gentamicin:*** Gentamicin inhibits many strains of staphylococci and coliforms and other gram-negative bacteria . Creams, ointments, or solutions gentamicin sulfate are for thetreatment of infected burns, wounds, or skin lesions.
3. Amikacin & others

Other Common used Antibiotics

1. **Chloramphenicol:** Chloramphenicol is a bacteriostatic broad-spectrum antibiotic that is active against both aerobic and anaerobic gram-positive and gram-negative organisms. It is active also against rickettsiae. *used for treatment of*

- *Typhoid and Paratyphoid*
- *invasive Salmonella infections*

- *pertussis* brain abscess and purulent meningitis (because of excellent penetration)

Side effects*:* The most important undesirable effect of **chloramphenicol** is its toxicity for bone marrow. It is manifested by anemia, leucocytopenia.

2. **Tetracyclines**: are classified as short acting (short acting : **Tetracycline**, or long-acting: **Doxycycline**) based on serum half-lives. *Used for treatment of* –

- *Gastroenteritis*
- *Bacilliary dysentery*
- *Anthrax and cholera*
- Respiratory, genitourinary or occular infections , epididymitis, cervicitis, some of pelvic inflammatory diseases, inclusion conjuctivitis and trachoma.

Adverse events: Gastrointestinal disorders of variable intensity are relatively frequent. Oral, intestinal, candidial super infection is a frequent consequences, permanent teeth discoloration develops related to the total amount of absorbed tetracycline.

3. **Erythromycin:** Erythromycin is poorly soluble in water but dissolves readily in organic solvents. Erythromycin is effective against gram-positive organisms, especially pneumococci, streptococci, staphylococci, and corynebacteria. Mycoplasma, Legionella, Chlamydia trachomatis, Helicobacter and others.

4. **Nalidixic acid**: Nalidixic acid is the first antibacterial quinolone. It is not fluorinated and is excreted too rapidly to have systemic antibacterial effects. These agents were useful only for the treatment of urinary tract infections and shigellosis.

- **NITROFURANTOIN:** Its Bacteriocidal drug, good effect against Enterobacteria (E.coli, Klebsiella, Enterobacter, ….) . Used for theatment and prophylaxis of urinary tract infections.

Adverse events: allergy, gastrointestinal disorders, neuropathy, autoimunne pneumonitis. The drug must not be used in gravid women

Vitamins

Overview

- Vitamins are organic compounds that regulate metabolism and make possible more efficient use of carbohydrates, proteins, and fat within the body.
- Vitamins themselves are totally lacking in caloric value.
- They do not provide any energy or serve as building materials.
- Vitamins enable the body to function in an orderly fashion, as most serve as coenzymes. The total amount of vitamins that a healthy person normally requires is minute.
- A well-balanced diet will provide ample vitamins for usual needs.

Types and classification of vitamins

Vitamins are usually classified on the basis of their solubility as either fat-soluble or water-soluble.

1- **Fat-soluble vitamins** are absorbed along with ingested dietary fats by the small intestines. The fat-soluble vitamins are A, D, E, and K.

2- **Water-soluble vitamins** by contrast, are absorbed along with water in the gastrointestinal tract and dissolve in the body fluids. The water-soluble vitamins are vitamin C (ascorbic acid) and the family of B vitamins.

Notice: Water-soluble vitamins cannot be stored in the body, so you need to get them from food every day. They can be destroyed by overcooking.

Fat-Soluble Vitamins

1. **Vitamin A** (retinol & carotene)

- Functions: Necessary for the vision cycle process - adaption to light and dark; tissue growth, especially skin and mucous membranes; toxic in large amounts.
- Results of Deficiency: Night blindness, exophthalmia, susceptibility to epithelial infection, changes in skin and membranes in tooth formation
- Sources: Retinol (animal food): liver, egg yolk, cream, butter or fortified margarine, whole milk; carotene (plant food): green and yellow vegetables, fruits

2. **Vitamin D** (calciferol)

- Functions: Absorption of calcium and phosphorus, calcification of bones; toxic in large amounts
- Results of Deficiency: Rickets, faulty bone growth, poor tooth development
- Sources: Fortified or irradiated milk, sunshine, fish oils

3. **Vitamin E** (tocopheral)

- Functions: Anti-oxidant; normal growth; reproduction
- Results of Deficiency: breakdown of red blood cells, anemia, sterility
- Sources: Vegetable oils, vegetable greens

4. **Vitamin K** (menadione)

- Functions: Normal blood clotting; toxic in large amounts
- Results of Deficiency: Bleeding tendencies, hemorrhagic disease
- Sources: Leafy green vegetables, cheese, egg yolk, liver; intestinal bacteria synthesis – main source

Water-Soluble Vitamins

1. Vitamin C (ascorbic acid)

- Functions: Intercellular cement substance; firm capillary walls and collagen formation; helps prepare iron for absorption and release to tissues for red blood cell formation
- Results of Deficiency: Scurvy, sore gums, hemorrhages, especially around bones, tendency to bruise easily, fevers and infections, poor wound healing and tissue formation, anemia
- Sources: Citrus fruits, tomatoes, cabbage, potatoes, strawberries, melons, chili peppers, broccoli, chard, turnip greens, green peppers

2. B-Complex vitamins

a- Vitamin B1 (Thiamin)

- Functions: Normal growth; coenzyme in carbohydrate metabolism; normal function of heart, nerves, and muscle
- Results of Deficiency: Beriberi; GI: Loss of appetite, gastric distress, indigestion, deficient hydrochloric acid; CNS: Fatigue, neuritis, paralysis; CV: Heart failure,
- Sources: Yeast, meat, whole grains, nuts, peas

b- Vitamin B2 (Riboflavin)

- Functions: Normal growth; coenzyme in protein and energy metabolism.

- Results of Deficiency: wound aggravation, cracks at corners of mouth, glossitis, eye irritation and sensitivity to light, skin eruptions
- Sources: Milk, liver, enriched cereals

c- Niacin (nicotinic acid)

- Functions: Coenzyme in energy production; normal growth, health of skin, normal activity of stomach, intestines, and nervous system
- Results of Deficiency: Pellagra; weakness, lack of energy, and loss of appetite; skin: scaly dermatitis; CNS: Neuritis, confusion
- Sources: Meat, peanuts, enriched grains

d- Vitamin B6 (Pyridoxine)

- Functions: Coenzyme in amino acid metabolism; protein synthesis, heme formation, brain activity.
- Results of Deficiency: Anemia; CNS: Hyperirritablity, convulsions, neuritis
- Sources: Wheat, corn, meat, liver

e- Pantothenic acid

- Functions: Coenzyme in formation of fat, cholesterol, and heme formation, and amino acid activation
- Results of Deficiency: Unlikely because of widespread occurrence and intestinal baceria synthesis
- Sources: Liver, eggs, milk, beef, cheese, legumes, broccoli, kale, sweet potatoes, yellow corn; also, intestinal bacteria synthesis

f- Folic acid

- Functions: Growth and development of red blood cells
- Results of Deficiency: Certain types of anemia; megoblastic (large, immature red blood cells)
- Sources: Liver, green leafy vegetable , eggs

g- **Vitamin B12** (Cobalamin)

- Functions: Normal red blood cell formation, nerve function, and growth
- Results of Deficiency: Pernicious anemia
- Sources: Liver, meats, milk, eggs, cheese

Drugs acting on the blood

INTRODUCTION

Hematopoiesis, the production of circulating erythrocytes, platelets and leukocytes from undifferentiated stem cells, is a remarkable process that produces over 200 billion new cells per day in the normal person and even greater number of blood cells in people with conditions that causes loss or destruction of blood cells. The hemopoietic machinery resides primarily in the bone marrow in adults, and requires constant supply of three essential nutrients – iron, vitamin B12 and folic acid

Anemia: a deficiency in oxygen carrying erythrocytes and very common in developing countries In this section anemia due to deficiency of iron, Vitamin B12 or a folic acid will be dealt with.

Agents used in Anemia

1. IRON

Hemoglobin that reversibly binds oxygen and provides the critical mechanism for oxygen delivery from lungs to other tissues. In the absence of adequate iron, small erythrocytes with insufficient hemoglobin are formed resulting in microcytic hypochromic anemia.

Causes of Iron Deficiency Anemia

1. Nutritional deficiency: Low intake of iron containing foods, reduced absorption as a result of mucosal damage.

2. Chronic blood loss: Chronic nose bleeding, GI bleeding, Worm infestation and Ulcers.

Daily requirement of Iron

- Male 10mg
- Female 15 mg

Increases in growing children, pregnant and lactating women

Sources

- Dietary - mostly in the organic form from meat, cereals, etc.

Absorption

Iron is absorbed in duodenum and proximal jejunum. A normal individual with out iron deficiency absorbs 5-10 % of daily intakes.

Storage: Iron is stored primarily as **ferritin** in intestinal mucosal cells and in macrophages in the liver, spleen and bone marrow.

Elimination:

Very small amount are execrated in stool by exfoliation of intestinal mucosal cells and trace amounts are execrated in bile, urine and sweat with total daily excretion not more than 1mg/day.

Treatment of Iron deficiency

Treatment of iron deficiency anemia consists of administration of oral or parenteral iron preparation.

1. Oral Iron Therapy: Only ferrous salts should be used because of most efficient absorption. Ferrous sulfate, ferrous gluconate, ferrous fumarate are the most commonly used oral iron preparations.

Side effects: Oral iron therapy can cause nausea, vomiting, epigastric discomfort, abdominal cramps, constipation and diarrhea.

2. Parenteral iron therapy:

- Iron dextran (Jectofer)

- Iron sorbitol

They may be given by deep IM or occasionally IV. Intravenous administration may result in very severe allergic reactions and thus should be avoided if possible.

Side effect: include local pain, tissue staining, headache, light headedness, fever, arthralgia, nausea, vomiting, urticaria, back pain, bronchospasm, and rarely anaphylaxis and death.

Vitamin B12: Daily vitamin B12 requirement is 2-5 mg. It is mainly obtained from animal products and serves as a co factor for essential biochemical reaction in humans. Ultimate source of vit B12 is from microbial synthesis. Absorbed in distal ileum after combined with intrinsic factor secreted by stomach .

Excess vitamin B12 is transported to the liver for storage and excreted in the urine.

Clinical uses: - Vit B12 is used to treat or prevent deficiency of vit B 12 and Pernicious anemia

Deficiency of Vit B 12 results in

1. Megaloblastic anemia
2. Neurological syndrome involving spinal cord and peripheral nerves

Folic Acid

Folic acids are required for essential biochemical reactions that provide precursors for the synthesis of amino acids and DNA. Daily requirement is 50 -100μg. Folic acid deficiency is not uncommon.

Sources: Include yeast, liver, kidney and green vegetables.

Deficiency: Common among elderly patients, poor patients, pregnant ladies. It results in megaloblasiic anemia. Congenital malformation in newborn like spina bifida are also consequences of folate deficiency during pregnancy. Folic acid given 1mg orally per day.

Drugs used in Disorder of coagulation

Homeostasis is spontaneous arrest of bleeding from a damaged blood vessel. Steps: Vascular injury , vasospasm, platelet adhesion, platelet aggregation , coagulation cascades fibrin formation.

Anticoagulants are the drugs which inhibit fibrin formation.

Classification

Based on mechanism of action

1. Fast and direct acting : e.g. **Heparin**
2. Slow and indirect acting Oral anticoagulants: e.g. **Warfarin and Dicumarol**

Heparin

It is inhibits the formation of fibrin clots, inhibits the conversion of fibrinogen to fibrin, and inactivates several of the factors necessary for the clotting of blood. Heparin works by inhibiting the three major clotting factors (thrombin, thromboplastin, and prothrombin)

Clinical Uses of Heparin

1. Prevention and treatment of venous thrombosis
2. Atrial fibrillation with embolus formation
3. Prevention of post operative thrombosis and embolism, in open heart surgery, in arterial embolus.
4. Acute myocardial infarction and peripheral arterial embolism

Side effects: Bleeding is the major side effect, allergy, osteoporosis

Warfarin

It is the most widely used **coumarin** anticoagulant and may be considered to be the drug of choice as an oral anticoagulant.

Mechanism of action

• The anticoagulant prevents reductive metabolism of the inactive vitamin K.

Clinical uses

1. Prevention and treatment of deep vein thrombosis.
3. treatment of atrial fibrillation with thrombus formation.
4. prevention and treatment of pulmonary embolus.

Side effects

Birth defect in pregnancy, hemorrhagic disease of newborn, hemorrhagic infarcts and cutaneous necrosis thrombolytics.

ASPIRIN (ASA)

Drugs that antagonize this pathway interfere with platelet aggregation and prolong bleeding time.

***Therapeutic Uses**:*

Prophylaxis against myocardial infarction and prevention of stroke in patients at risk, e.g. those with transient ischemic attacks.

Adverse Effects

Gastrointestinal The gastritis that occurs with aspirin may be due to irritation of the gastric mucosa by the un dissolved tablet

Central Nervous System Effects: With higher doses, patients may experience

Drugs acting on central nervous system

This group include

1- Analgesics
2- Anxiolytics
3- Sedative
4- Hypnotics
5- Anti-epileptics

Analgesics (pain medication)

Analgesics refer to a group of drugs used to temporarily relieve pain. They are sometimes known as painkillers. They block pain signals by changing how the brain interprets the signals and slowing down the central nervous system, prescribed or illegal drugs can create dangerous and unpredictable effects. There are two main types of analgesics: non-narcotic and narcotic.

Types of Analgesics

A- ***Non-narcotic Analgesics:*** There are two major types:

- Acetaminophen (Paracetamol®)
- Non-steroidal anti-inflammatory drugs

1. **(ASA (Aspirin®)**
2. **Ibuprofen (Profen®)**
3. **Naproxen**
4. **Mefenamac acid (Ponstan®)**
5. **Diclofenac (Volatrin)& others**

- Used to reduce pain from headache, cold, flu, arthritis and many other conditions.
- Recommended dosage is to repeat every 4 to 6 hours (if needed) with no more than 6 or 8 capsules or tablets taken within a 24 hour period.
- These drugs can be a safe and effective method of reducing pain and fever.

Non-Steroidal anti-inflammatory drugs (NSAIDs)

- Are useful for relieving pain, fever and inflammation.
- Acetyl salicylic acid (ASA) **(Aspirin)** has a stronger anti-blood clotting effect, making it useful as a blood thinner.
- One of the major drawbacks of NSAIDs is that they can cause stomach irritation and in some cases frequent use causes ulcers or internal bleeding. For this reason, pharmacists recommend taking them with meals. For those people, who cannot tolerate NSAIDs, it is suggested they take acetaminophen

B- Narcotic Analgesics

- Narcotic analgesics are also known as **opioid** analgesics.
- They are used in medicine as strong analgesics, for relief of severe or chronic pain.

- Some **opioids**, such as morphine and codeine are made from opium, a thick white liquid extracted from the unripe seeds of the opium poppy, which grows in southern Asia.

General Side effects due to analgesics

• drowsiness, sedation
• dizziness, loss of balance
• blurred vision
• dry mouth
• nausea, vomiting, constipation, loss of appetite
• headache
• itching
• sweating
• difficulty with urination
• anxiety, depression
• hallucinations
• tremors…..etc .

Sedative & Hypnotic drugs

Anxiolytic drugs are used to treat the symptoms of anxiety, where as **hypnotic drugs** used to treat insomnia. The same drugs are used for both purposes.

Classes of anxiolytic and hypnotic drugs: The main groups of the drugs are:

1. ***Benzodiazepines.*** Benzodiazepines are the most important group, used as sedative and hypnotic agents.

2. ***Barbiturates*** (phenobarbitone). They are nowadays less commonly used as sedativehypnotics.

3. **β *-adrenoceptor antagonists* (e.g. propranolol).** They are used to treat some forms of anxiety, where physical symptoms (sweating, tremor, and tachycardia), are troublesome. They are not used as hypnotics.

4. *Miscellaneous drugs* (chloral hydrate, paraldehyde, and diphenhydramine).

Benzodiazepines

Benzodiazepines are well absorbed when given orally. They bind strongly to plasma proteins. Benzodiazepines are inactivated by the liver and excreted in the urine. medium acting (alprazepam, lorazepam) and long acting compounds (diazepam, chlordiazepoxide, clonazepam).

Clinical Uses

- Treatment insomnia
- Anxiety
- Preoperative mediations
- Acute alcohol withdrawal
- As anticonvulsants
- Chronic muscle spasm and spasticity

Unwanted effects of Benzodiazepines

- Toxic effects due to acute overdosage causes prolonged sleep.
- Unwanted effects occurring during normal therapeutic use includes: drowsiness, confusion, amnesia, and impaired motor coordination.

• Tolerance and dependence:

Barbiturates

They are non-selective CNS depressants, which produce effects ranging from sedation and reduction of anxiety. It less specific than benzodiazepines. Tolerance and dependence occur, more than benzodiazepines.

Antiepileptic drugs

Seizure *is* associated with the episodic high frequency discharge of impulses by a group of neurons in the brain. Seizure may be partial or generalized depending on the location and the spread of the abnormal neuronal discharge. The attack mainly involves motor, sensory or behavioral phenomena.

Partial seizures are often associated with damage to the brain, whereas generalized seizure occurs without obvious cause. Two common forms of generalized seizures are grand mal and petit mal.

Anticonvulsant drugs act by reducing electrical excitability of cell membrane in the brain. The main drugs used in the treatment of epilepsy are

- **Phenytoin**
- **Carbamazepine**
- **phenobarbitone.**

Phenytoin

It is commonly used antiepileptic drug. It is effective against different forms of partial and generalized seizures; however it is not effective in absence seizures. Well absorbed when given orally. It is metabolised by the liver.

Carbamazepine (Tegretol)

Its pharmacological action resembles those of phenytoin, however, it is chiefly effective in the treatment of partial seizure. It is also used in the treatment of trigeminal neuralgia and manic-depressive illness.

Antipsychotic drugs

Psychotic illness is characterized by delusion, hallucinations, thought disorder, social withdrawal and flattering of emotional response. Antipsychotics are a group of drugs used mainly for treating schizophrenia.

Antipsychotic agents are classified into

- **Chlorpromazine**
- **Haloperidol**
- **Clozapine**

Most antipsychotic drugs are readily but incompletely absorbed.

Clinical uses

• Schizophrenia

• Mania

• Vomiting

Adverse Reactions

• Seizures
• Autonomic nervous system effects (orthostatic hypotension)
• Metabolic and Endocrine Effects (weight gain, hyperprolactinemia, infertility)

Antidepressant drugs:

Depression is one of the most common psychic disorders. Antidepressants are the drugs which are mainly used in the management of depression.

- An **antidepressant** is a psychiatric medication used to alleviate mood disorders, such as major depression and anxiety disorders such as social anxiety disorder.
- **Amitriptyline** (Tryptizol), Imipramine (Tofranil), Nortriptyline (Allegron).....etc.
- **Adverse effects:** sleepiness, dry mouth, increased hunger, cardiac arrhythmias and changes in BP

Endocrine Pharmacology

I. Anti- diabetic drugs

INTRODUCTION

Diabetes Mellitus *is a* disease that occurs as a result of absolute or relative deficiency of insulin that results in metabolic and vascular abnormalities. The ***etiologies*** include Obesity (because chronic calorie intake and prolonged stimulation of β cell causes a decrease in insulin receptor and also adipose tissue and muscle are less sensitive), hereditary,damage of pancreatic tissue, diabetogenic hormones(like growth hormone, thyroid, epinephrine), diabetogenic drugs like Thiazide diuretics, epinephrine, phenothiazines ,Other factors like Pregnancy. It can *be* ***classified*** *as:*

- Type I: ***insulin dependent diabetes mellitus (IDDM)*** *(*or Juvenile type) occurs predominantly in children and young adults who have no insulin secretion
- Type II: ***non dependent diabetes mellitus (NIDDM)*** (or maturity onset type) usually occur after the age of 40years.

Antidiabetogenic drugs

I. Insulin

Sources : include pork or beef, combination of pork and beef and also human insulin (Recombinant DNA technique)

Actions: - Insulin lower blood glucose level through increasing utilization of glucose by peripheraltissue and promoting synthesis and storage of glycogen.

- The main actions of the hormone are exerted on metabolism of carbohydrate (CHO), fat and protein in liver, muscle & adipose tissue.

Therapeutic use - IDDM, NIDDM (not controlled by diet and oral hypoglycemic agents), diabetic ketoacidosis, Control of diabetes in pregnancy, during surgery and in infections.

Adverse Reaction: can be categorized as

Local: Atrophy or hypertrophy at site of injection, local hypersensitivity and secondary infections.

Systemic: Hypoglycemic coma and Immunologic reaction.

II. Oral Hypoglycemic: These are drugs administered orally to lower blood glucose level used in mild diabetes. They are grouped as **Sulphonylureas** and **Biguinides**.

1. **Sulphonylureas:** These compounds are chemically related to sulphonamides.

Glibenclamide (Doanil)

Mechanism: hypoglycemic action is due to Stimulation of insulin release from β cell, Depression of glucagon secretion, Increase number of insulin receptor, Reduce insulin output from liver (Decrease hepatic gluconeogenesis and glycogenolysis)

- They are rapidly absorbed from the gastrointestinal tract.
- They are also extensively plasma protein bound and are mainly metabolized in the liver.

Use: Mild diabetes mellitus in old patients (type II)

Side effects: Gastric irritation, prolonged hypoglycemia (esp. chlorpropamide), large doses confusion, vertigo, ataxia, leucopenia, aggranulocytosis, thrombocytopenia, and teratogenecity

2. **Biguinides:** They potentiate the hypoglycemic action of insulin and sulphonyl ureas but they don't produce clinical hypoglycemia in diabetics. **Biguanides** include drugs like **metformin** and **phenformin**

***Mechanism*:** They do not stimulate the release of insulin. They increase glucose uptake in skeletal muscle, and have effects on glucose absorption and hepatic glucose production.

- **Phenformin** and **Metformin** are rapidly absorbed from the gastrointestinal tract.
- **Metformin** is largely excreted unchanged in the urine and has a longer duration of action.

***Side effects*:** Nausea, vomiting, anorexia, diarrhea, abdominal cramp, lactic acidosis (esp. phenformin)

***Use*:** Obese diabetics (uncontrolled by diet alone), Supplement to sulphonyl urea

Lipid-lowering drugs

- Several drugs are used to decrease plasma LDL-CHO
- Drug therapy to lower plasma lipids is only one approach to treatment
- and is used in addition to dietary management and correction of other modifiable cardiovascular risk factors

Lipid Lowering Drugs: Statins

HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors. The reductase catalyses the conversion of HMG-CoA to mevalonic acid; blocks the synthesis of CHO in the liver:

Simvastatin + pravastatin + atorvastatin

- decrease hepatic CHO synthesis
- lowers total and LDL Stimulates the exprssion of more enzyme
- → restores CHO synthesis to normal.
- well absorbed when given orally
- extracted by the liver (target tissue), undergo extensive presystemic biotransformation

***Adverse effects*:** myopathy (incr in pts given combined therapy with nicotinic acid or fibrates. Should not be given during pregnancy.

Simvastatin

Adverse effects: mild gastrointestinal disturbances, increased plasma activities in liver enzymes, severe myositis and angio-oedema (rare)

clinical uses

- Secondary prevention of myocardial infarction and stroke in patients who have symptomatic atherosclerotic disease (angina, transient ischemic attacks) following acute myocardial infarction or stroke.

- Primary prevention of arterial disease in patients who are at high risk because of elevated serum CHO concentration, especially it there are other risk factors for atherosclerosis

Atorvastatin lowers serum CHO in patients with homozygous familiar hypercholesterolemia

Endocrine pharmacology

I .Oxytocics: These are group of drugs that cause contraction of the uterus.

Oxytocin

Actions:

1. Oxytocin stimulates the uterus and cause physiologic type of contraction

2. It also causes ejection of milk through contraction of the myo-epithelial cells around the alveoli of the mammary gland.

***Use*:** Induction of labor in women with uterine inertia, Relief of breast engorgement during lactation (few minutes before breast feeding) as nasal spray, Postpartum hemorrhage.

***Side effect*:** Oxytocin may cause over stimulation and leads to rupture of the uterus in the presence of cephalo-pelvic disproportion.

Prostaglandins: They induce labor at anytime during pregnancy but most effective at the third trimester. In female reproductive system prostaglandin E & F are found in ovaries, endometrium and menstrual fluid which is responsible for initiating and maintaining normal birth process.

Adverse reaction: nausa, vomiting, headache, diarrhea, fever, etc.

II. Female Sex Hormones and Hormonal Contraception

Oestrogens

These drugs can be classified into three groups.

1. Natural – **estradiol, esterone, estriol**

2. Semisynthetic – **Ethnylestradiol**

3. Synthetic: **Diethylstibosterol**

Natural

Estradiol*:* Estradiol is most potent, major secretory product of ovary.It is oxidized into esterone .

Semisynthetic

Ethylestadiol: Highly potent, effective orally

Absorption and Fate: It is absorbed from GI and skin and rapidly metabolized in the liver

Physiologic actions:

Genital system

Ovary: estrogen affects the ovary through indirectly influencing the secretion of gonadotrophin

Uterus: it affects the 'proliferative phase' of the endometrium and also increases the growth and sensitivity of myometrium for oxytocin.

Cervix: it makes cervical mucus thin and alkaline

Vagina: Stratification, cornification and glycogen deposit is affected by estrogen.

Breast: Estrogen causes the growth of gland and duct system

Anterior pituitary: Estrogen inhibit release of gonadotrophins (FSH, LH)

Therapeutic use: contraceptive in combination with progestogens, Functional uterine bleeding, Dysmenorrhea, Alleviation of menopausal disorder, Osteoporosis, Replacement therapy in ovarian failure, Prevents senile and atrophic vaginitis

Side effects: Thromboembolism, Sodium and water retention, nausea, endometrial carcinoma

Progestogens

Progestrone is natural occuring progestational hormone. It is synthesized by corpus luteum, placenta, adrenal cortex, testis. It is less effective orally due to complete metabolism by liver so it's given through intramuscular route.

*Actions on g*enital organs:

Ovary: Inhibition of ovulation

Uterus : converts the endometrum for secretory phase and makes the myometrium less sensitive to oxytocin. It also causes relaxation of the uterus in late pregnancy.

Therapeutic use: Hormonal contraception**,** functional uterine bleeding**,** dymennorrhea **,** Endometrial Carcinoma **.**

Oral Contraceptives

These are drugs taken orally to prevent conception. They are available in the following forms:

1. Combined regimen type
2. Sequential regimen type
3. Triphasic pill regimen

Combined regimen: involves the administration of pills containing combination of **Estrogen** and **Progestogen**. They are administered starting 5th day of menstrual cycle for 21 days. In biphasic and triphasic pills: these are combined oral contraceptive pills containing varying proportion of an estrogen and a progesterone designed to stimulate the normal pattern of menstrual cycle.

Mechanism: includes inhibition of release of FSH and LH, increase viscosity of cervical mucus endometrial changes, interfere with contraction of cervix, uterus and fallopian tube

Preparation

i) Oral progesterone : **Norethindone (Norgestril)**

ii) Medroxyprogestrone acetate **(Depoprovera®):** IM injection of long acting progestogen.

iii) **L – norgestril (Norplant®):** Subcutaneous implant :

Mechanism*:* It makes cervical mucus thick, though & hostile and also alter endometrial wall

Side effects of oral contraceptive: Thromboembolic complication, Weight gain & fluid retention, Menstrual disorder, Breast tenderness & fullness, Skin changes, Nausea & vomiting, Depressed mood, Reduced lactation

Beneficial effects of estrogen /progesterone oral contraceptive

1) Reduced risk of endometrial Carcinoma, ovarian cyst
2) regular Menses, No excessive blood loss
3) Less premenstrual tension and dysmenorrheal.
4) Relief of endometriosis

Adrenocortical Hormones

Adenocortical hormones control the metabolism of carbohydrate (CHO), protein, fat and water /electrolytes

Adencortical hormones are classified into:

a) Glucocorticoid – Cortisone, Hydrocortisone (Cortisol)

b) Mineralocorticoid - Aldosterone

c) Sex Hormone – Estrogen, Androgen

They are classified as

1. **Short acting** e.g cortisone, hydrocortisone
2. **Intermediate acting** e.g predinsolone, triamcinolone
3. **Long acting** e.g dexamethasone, betamethasone)

Dexamethasone & **betamethasone** have got a high glucorticoid activity while cortisone and hydrocortisone have high mineralocorticoid action. Therapeutic activity in inflammatory disorder is proportional to the glucocorticoid activity.

***Calcium metabolism*:** increased Ca++ excretion, interfere with Ca++ absorption

Therapeutic use

1) Replacement therapy: In **Addisons disease**

2) **Antinflammatory:** in conditions like Collagen disease (rheumatoid carditis, arthritis),

3) **Hypersensitivity reactions**: (Bronchial Asthma, status asthmatic), Blood disease due to circulating antibodies (autoimmune disease), Skin disease (eczema), Eye disease (allergic inflammation of the eye), Nephrotic syndrome, Acute gout.

4) **Immunosuppression:** In tissue / organ transplantation.

Side effects:

- Due to prolonged use: Weight gain and edema hypo-kalmia, hyperglycemia, osteoporosis, psychiatric disturbance, susceptibility to infection (like TB), peptic ulceration, Cushing syndrome, retarded growth

Thyroid and Antithyroid Drugs

They inhibit the function of the thyroid gland and used in hyperthyroidism.

Antithyroid drugs include:

1. Thiourea compounds, e.g **methimazole, carbimazole**
2. Ionic inhibitors, e.g. , **potassium percholate**
3. Iodide, e.g. **potassium iodide**
4. Radioactive iodine (131I)

Thiourea Compounds

Inhibit the formation of throid hormone through inhibiting the oxidation of iodide to iodine by peroxidase enzyme and blocking the coupling of iodothryosines to form iodothyronines.

- They are contraindicated in pregnant and lactating women.

- Toxicities include drug fever, skin rashes, increased size and vascularity of the thyroid gland.

Ionic Inhibitors

Potassium percholate prevents the synthesis of thyroid hormones through inhibition of uptake and concentration of iodide by the gland.

Iodides

Improve manifestations of hyperthyroidism by decreasing the size and vascularity of the gland so they are required for preoperative preparation of the patient for partial thyroidectomy.

Radioactive Iodine:

It is used in hyperthyroidism as sodium 131I orally. It is contraindicated in pregnancy and lactation as it affects thyroid gland in the fetus and the infant.

Toxicology

Toxicology is concerned with the deleterious effects of chemical and physical agents on all living systems.

The terms poison, toxic substance . The most important axiom of toxicology is that "the dose makes the poison", indicating that any chemical or drug can be toxic if the dose or exposure becomes high enough.

1. Poisoning occurs by non-therapeutic substances such as household and environmental agents, and due to over-dosage of therapeutic substances.
3. Poison may be ingested accidentally or deliberately.
5. A toxic response can occur within minutes or after a delay of hours, days, months or years.

General measures in poisoning

The treatment of a poisoned patient requires a rapid and genuine approach. There are three principles underlying the management of poisoning:

1. Life support
2. Drug identification
3. Drug detoxification
4. The effectiveness of the approaches employed for detoxification may depend on the **route of administration** of the poison.
5. Emesis is contraindicated after ingestion of corrosive chemicals.
6. More invasive procedures such as gastric lavage and haemodialysis can be performed.
7. Antidotes are available against poisoning with the following substances and are able to reverse the toxic manifestations.

Toxicity in some heavy metals

1. Metals May be found as essential elements in the body, in the environment, food or workplace.
2. Exposure to metals occurs through the continuum from mining, extraction of ore, refining, manufacturing, or disposal.
3. Target organ can be the site of contact.
4. Ability of metal to cross membranes (example lungs, GI tract) varies greatly.
5. Toxicity varies greatly from metal to metal. Example aluminum vs. mercury

Biological Activity of poisoning with heavy metals

- Inhibit enzymes
- Displaces an essential metal cofactor in the enzyme, vitamins and substrate
- Inhibit synthesis of proteins

- Substitutes for essential metals

Notices

- Dietary factors: low levels of protein in the diet or deficiencies of vitamins C and D can impact uptake
- Old and young at greatest risk
- Lead and mercury can cross the placenta barrier
- Some metals may be found in blood, hair, nails and other excreta

Site of injury and metals

- **Renal excretion** (kidney) is the primary means by which the body rids itself of metals.
- Kidney is often the site of injury from metals and metabolites
- GI tract also an important route of excretion
- Inorganic **Hg, Pb, Cr & Pl** leading to proximal tubule damage.

Mercury poisoning

Source of mercury poisoning :

- Air and water are small sources of mercury with respect to human exposure.
- Fish is the highest single source of Hg in food like Tuna and swordfish

Lead poisoning

Through human activities such as mining, smelting, manufacturing, and recycling, lead finds its way into the air, water, and surface of soil. Lead-containing manufactured products (gasoline, paint, printing inks, lead water pipes, lead-glazed pottery, lead-soldered cans, battery casings, etc.) also contribute to the lead burden. Lead in contaminated soil and dust can find its way into the food and water supply. The toxic effects of lead occur in many tissues of the body.

Organ systems impacted by lead

- Hemopoietic (blood forming organs)
- Nervous system
- GI tract
- Kidneys
- Reproductive tract.

Specific antidotes for poisoning with substances.

No.	Substance	Specific Antidote
1	**Paracetamol**	*Acetylcysteine, methionine*
2	**Anticholinesterases**	*Atropine, pralidoxime*
3	**Iron**	*Desferrioxamine*
4	**Benzodiazepines**	*Flumazenil*
5	**Heparin**	*Protamine sulfate*
6	**Warfarin**	*Vitamin K1*
7	**Digoxin**	*Digoxin-specific antibodies*
8	**Methoanol**	*Ethanol*
9	**CO**	*O2*
10	**Lead**	*Calicum disodium edetate*

11	**Arsenic, gold, mercury**	*Dimercaprol*
12	**Copper, Zinc, gold**	*D-penicillamine*