PHARMACOLOGY-II

UNIT 2 NOTES

CARDIOVASCULAR SYSTEM

- Therapy of Shock
- Hematinics, Coagulants & Anticoagulants
- Fibrinolytics and Anti Platelet Drugs
- Plasma Volume Expanders

URINARY SYSTEM

- Diuretics
- Anti Diuretics

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SHOCK

- Shock is defined as a life threatening medical condition where body is not getting enough blood flow, leading to lack of oxygen & nutrients needed for organs & tissues to function properly.
- This can result in severe damage and if untreated, can lead to organ failure & death.

TYPES OF SHOCK

It can be further divided into following types :

① Hypovolemic Shock
② Cardiogenic Shock
③ Septic Shock
④ Anaphylactic Shock
⑤ Neurogenic Shock

Hypovolemic Shock

It is defined as loss of significant amount of blood or fluids due to severe bleeding (internal or external), reducing the blood volume circulating in the body

Cardiogenic Shock

It occurs due to failure of heart to pump blood effective due to Heart attack, Heart failure leading or arrythmias leading to inadequate perfusion of tissues.

Sepic Shock

It is triggered by severe infection, leading to systemic inflammation and vasodilation.

Anaphylactic Shock

It is caused by severe allergic reactions that leads to widespread vasodilation & airway obstruction.

Neurogenic Shock

Neurogenic shock is a type of distributive shock that occurs when nervous system is damaged or impaired, leading to loss of sympathetic tone & vasodilation results in a sudden & severe drop of blood pressure, reducing blood flow to vital organs.

CAUSES

- Hemorrhage
- Burns
- Dehydration
- Severe Diarrhea
- Myocardia Infarction
- Heart failure
- Trauma / Injury
- Infections etc.

Symptoms

- Hypotension
- Pale skin
- Rapid Breathing
- Rapid Heart Rate
- Cold Skin
- Confusion / Altered Mental State
- Weakness / Fatigue
- Reduced Urine Output
- Loss of Consciousness

Drugs Used In Therapy Of Shock

The drugs used in the treatment of shock can be divided into following classes :

- Sympathomimetic Amines
- α- adrenoreceptor blocking agents
- Corticosteroids
- Oxygen
- Cardiac Glycosides
- Glucagon
- Dextrans.

SYMPATHOMIMETIC AMINES

Sympathomimetic Amines are a class of drugs that mimic the effects of sympathomimetic nervous system.

Mechanism of Action

Sympathomimetic amines act on adrenergic receptors (α & β) to produce effects similar to sympathetic nervous system.

- Increased hear rate & contractility
- Increase blood pressure
- Increase respiratory rate etc.

Adverse Effect

- Tachycardia
- Arrythmias
- Ischemia
- Increased O_2 demand

Application

- Septic Shock
- Cardiogenic Shock
- Anaphylactic Shock
- Neurogenic Shock

Example of Drugs

Epinephrine, Nor- Epinephrine, Dopamine, Dobutamine, Phenylephrine, Vasopressin, Isoprenaline, Metaraminol etc.

SOME INDIVIDUAL DRUGS

① Adrenaline

- It acts on both α & β receptors.
- It used as a first line drug in anaphylactic shock
- It can be used in cardiogenic shock when other agents are insufficient
- It increases blood pressure and cardiac output.

② Nor- Adrenaline

- It primarily stimulates α1 receptor
- It is used as first line drug in septic shock
- It restores blood pressure by increasing vascular resistance.
- It also increases cardiac output by enhancing heart contractility.

③ Dopamine

- It stimulates dopaminergic, α_1 & β_1 receptors.
- In low doses: Activates dopaminergic (D_1) receptors, promoting renal vasodilation & increased urine output.
- Moderate doses: Stimulates β_1 receptors, increasing heart rate & contractility.
- High Doses: Stimulates α_1 receptors, causing vasoconstriction.
- It increased cardiac output & blood pressure depending on dosage.

α- ADRENORECEPTOR - BLOCKING AGENTS

Alpha adrenoreceptor blockers, are medications that block the effect of sympathatic nervous system on α- receptors
In shock therapy α- blockers are used to :

- Reduce Peripheral vascular resistance.
- Increase blood flow to vital organs.
- Decrease blood pressure.

Mechanism Of Action

Alpha- blockers inhibit the action of catecholamines on α- receptors leading to :

- Vasodilation
- Increased blood flow
- improove cardiac output
- Increase oxygen delivery to tissues

Adverse Effect

- Hypotension
- Reflex Tachycardia
- Fluid Retention

Uses

- Septic Shock
- Cardiogenic Shock
- Anaphylactic Shock
- Neurogenic Shock

Examples

- Phentolamine
- Prazosin
- Terazosin

CORTICOSTEROIDS

- Corticosteroids are agents that are primarily used in the management of septic shock.
- They are class of steroid hormones produced by adrenal cortex & can be divided into two main categories :

① Glucocorticoids.
② Mineralocorticoids.

Mechanism Of Action

- Corticosteroids like Hydrocortisone, binds to glucocorticoid receptors in cytoplasm of target cells.
- This receptor - steroid complex then moves to the nucleus & regulate transcription of specific genes involved in body's inflammatory response, immune regulation & metabolic process.
- They reduce the transcription of pro-inflammatory genes & promote the expression of anti-inflammatory proteins thus reduce inflammation.

Example

- Hydrocortisone
- Methylprednisolone
- Dexamethasone

Risk & Side Effect

- Hyperglycemia
- Hypokalemia
- Hypertension
- Fluid Retention

OXYGEN

- Oxygen therapy is a fundamental part of treating shock, aimed at preventing tissue hypoxia & ensuring adequate oxygen delivery to meet metabolic needs of vital organs.
- It is essential across all types of shock, from hypovolemic and cardiogenic to septic and anaphylactic shock.
- The method of oxygen delivery varies depending on the severity of hypoxia and all type of shock, but its timely and appropriate use is critical to reduce the risk of organ failure and improving outcomes in shock management.

CARDIAC GLYCOSIDES

- Cardiac Glycosides are medications used to treat heart failure
- In context of shock, cardiac glycosides are used to:
- Increase cardiac contractility.
- Improve Cardiac Output
- Enhance Peripheral Vascular Resistance.

Mechanism Of Action

Cardiac glycosides inhibit sodium-potassium pump, leading to:

- Increased intracellular sodium
- Increased calcium availibility
- Enhance cardiac contractility
- Increase cardiac output
- Improve peripheral vascular resistance.

Examples

- Digoxin
- Digitoxin
- Ouabain

GLUCAGON

Glucagon plays a specific role in the management of certain types of shock :

① Hypoglycemic Shock

- In case of severe hypoglycemia, glucagon can rapidly increase blood glucose levels by stimulating glycogenolysis and gluconeogenesis in liver.
- This can help restore consciousness and stabilize the patients.

② β Blocker Overdose

- Glucagon can be beneficial in treating patients having overdose on β- Blockers.
- It acts independently of β- receptors, increasing heart rate & myocardial contractility.
- This can help improve cardiac output & blood pressure in such scenarios.

③ Potential Use In Other types of shock

while not a primary treatment, glucagon may also have a supportive role in other forms of shock, particularly when there is are associated metabolic derangements.

DEXTRANS

Dextrans are polysaccharides that are particularly used in the treatment of Hypovolemic shock, primarily due to their properties as volume expanders.

Mechanism Of Action

- Dextrans increase plasma volume by drawing water into the intravascular space through osmotic effects.
- This helps to restore blood volume & improve circulation during shock.
- By increasing blood volume, dextrans can enhance perfusion to vital organs, helping to stabilize patients in shock.

Clinical Uses

- Hypovolemic Shock
- Burn & Trauma Patients

Side Effects

- Allergic Reactions
- Coagulation Issues
- Fluid Overload

HAEMATINICS

- Haematinics are substances or drugs that are used ~~in~~ to increase haemoglobin level or enhance production of red blood cells, which are vital for carrying oxygen to tissues in body.
- They are typically used in treatment & prevention of anaemia caused by deficiency of iron, vitamin B12, folic acids & other nutrients necessary for blood formation.

KEY COMPONENTS OF HAEMATINICS

Haematinics mainly include :

- Iron
- Vitamin B_{12} (Cyanocobalamin)
- Vitamin B_9 (Folic Acid)

IRON

- Iron is the most essential element for blood production Deficiency of iron leads to iron deficiency anaemia, which is most common form of anaemia worldwide.
- About 70% of body's iron found in RBCs
- It is essential for production of Haemoglobin in RBCs which is essential for transferring oxygen in blood from lungs to tissues.

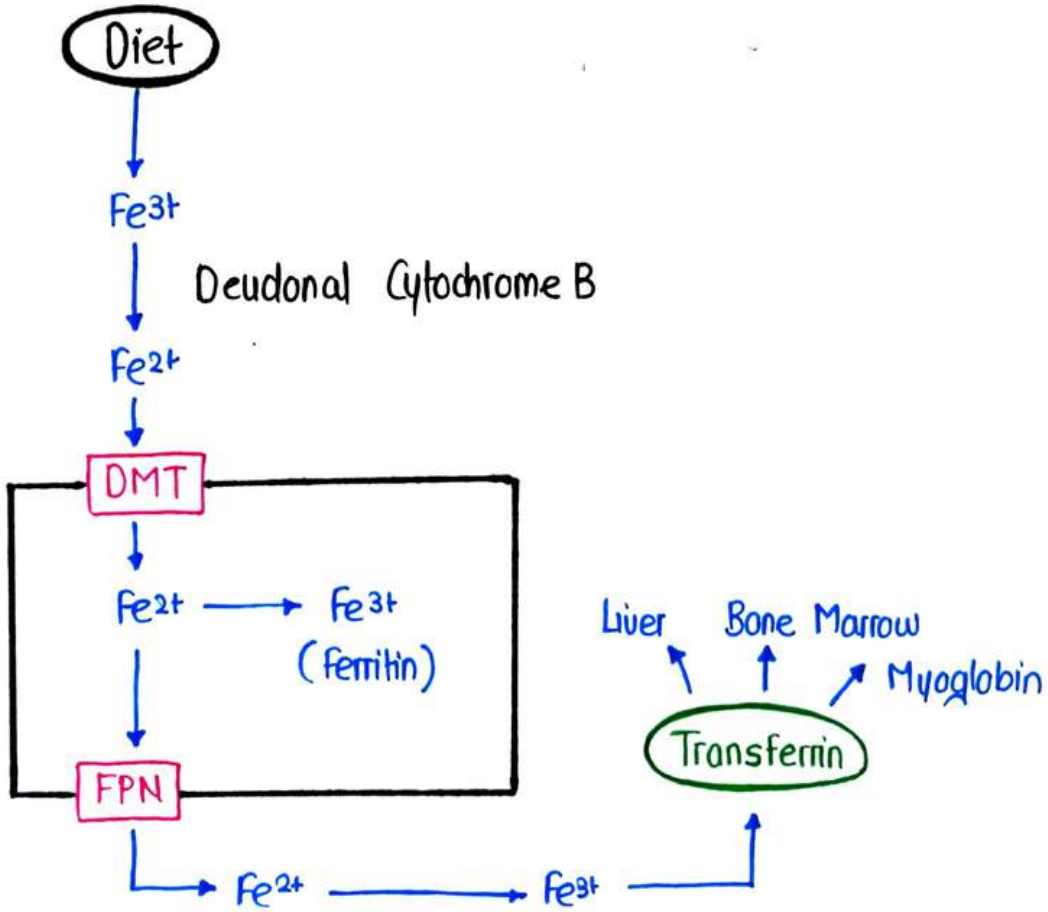
Daily Requirment

- Adult Male : 0.5-1 mg
- Adult Female : 1-2 mg

Dietary Sources

- Leafy Green Vegetables
- Pumpkin Seeds
- Tofu
- Red Meat
- Whole Grains etc

Iron Absorption, Storage & Utilization



Types Of Iron Used In Haematinics

① Oral Iron Preparations

- Ferrous Sulphate : It is most commonly used oral iron supplement due to its high bioavailibility .
- Ferrous Gluconate : less irritating to the gastrointestinal tract but with slightly lower bioavailibility .
- Ferrous Fumarate : Also a commonly used form with high iron content .
- Iron Polymaltose Complex : It is a newer form of iron supplement with fewer GIT issues .
- Carbonyl Iron : Pure elemental iron , often used to reduce side effects associated with other forms .

② Parenteral Iron Preparations

- Iron Dextran : Used intramuscularly or intravenously but has risk of allergic reactions .
- Iron Sucrose : Commonly used intravenously for patients with chronic kidney disease or severe anaemia .
- Iron Carboxymaltose : A newer intravenous form .

Adverse Effect Of Iron Supplements

- Nausea
- Vomiting
- Constipation
- Dark Stools

Iron Overload

Uses

- Iron deficiency anaemia
- Megaloblastic Anaemia.

VITAMIN B12

- Vitamin B_{12} is a water soluble vitamin essential for proper formation and maturation of RBCs and synthesis of DNA in bone marrow.
- Deficiency in vitamin B_{12} leads to megaloblastic anaemia
- It is essential for normal Erythropoeisis.

Functions Of Vitamin B_{12}

- It is essential for proper replication of DNA during RBCs formation. Essential for maintainance of myelin sheath around nerves, preventing neurological damage.
- Deficiency of vitamin B_{12} leads to megaloblastic anaemia where large, immature & non functional RBCs are produced.

Absorbtion & Utilization of Vitamin B_{12}

Diet

↓

Vitamin B_{12}

↓

Vitamin B_{12} + Haptocorrin (Salivary Gland)

↓ (Deudonum)

Vitamin B_{12} + Intrinsic Factor (Parietal Cells)

(Ileum) ↓

Vitamin B_{12} + Transcobalamin II → (Liver, Bone Marrow, Cells)

Sources

- Meat
- Fish
- Dairy Products
- Eggs

Forms Of Vitamin B_{12} Used as Haematinics

- Cyanocobalamin : It is the most common form of vitamin B_{12} used in supplements & injections.
- Hydroxocobalamin : Used for treating vitamin B_{12} deficiencies particularly in cases of pernicious anaemia.

Adverse Effect

Vitamin B12 has very few adverse effects, rarely, allergic reactions to the injection form may occur.

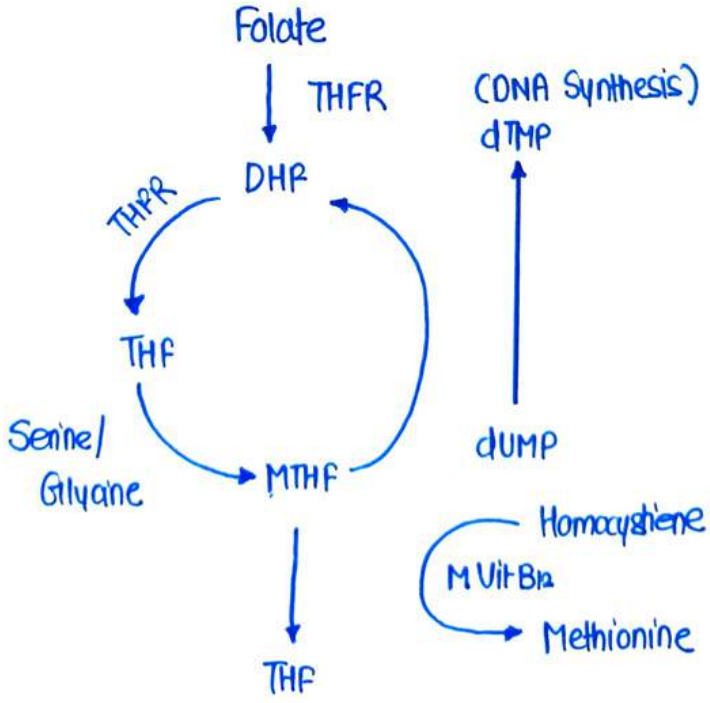
FOLIC ACID

- Folic Acid is essential for DNA synthesis & production of RBCs.
- Its deficiency leads to megaloblastic anaemia, similar to vitamin B12 deficiency.
- Folic acid is a combination of Pteridine nucleus + Para Amino Benzoic Acid + Glutamic Acid.

Functions Of Folic Acid

- DNA Synthesis : Acts as a coenzyme in the synthesis of nucleic acids, necessary for formation of RBCs.
- Cell Division : Particularly important in rapidly dividing cells like RBC precursor in bone marrow.

Folic Acid Metabolism



Dietary Sources

- Leafy Green Vegetables
- Citrus Fruits
- Beans
- Nuts

Forms Used as Haematinics

- Oral Folic Acids : Available as tablets & used as supplement in case of deficiency
- Leucovorin : A more potent form used in certain medical conditions like methotrexate toxicity.

Uses

- Megaloblastic Anaemia
- Pernitious Anaemia
- Folate Deficiency

Blood Clotting

- It is the main and final process of blood clotting.
- It is the process by which blood clot forms.
- It is a complex procedure of enzymatic reactions in the presence of various clotting factors which results in the formation of clot over the injured blood vessels.

- It can be divided into three pathways :

① Intrinsic Pathway
② Extrinsic Pathway
③ Common Pathway

Clotting Factors

NUMBER	FACTOR NAME
I	Fibrinogen
II	Prothrombin
III	Tissue Factor (Thromboplastin)
IV	Calcium Ions
V	Proaccelerin / Labile Factor
VII	Proconvertin / Stable Factor
VIII	Antihaemophilic Factor A
IX	Christmas Factor / Antihaemophilic Factor B
X	Stuart Factor / Prower Factor
XI	Plasma Thromboplastin / Antihaemophilic Factor C
XII	Hageman Factor
XIII	Fibrin stabilizing Factor

- Clotting factors always written in roman numbers.
- Factor VI is not in the existence

Intrinsic Pathway

- This is a complex pathway & occurs slowly.
- This pathway occurs due to blood trauma.
- In this pathway when blood vessel gets injured, then endothelial tissue inside blood vessel also gets damaged and blood comes in direct contact with collagen fibres of connective tissue present around the endothelial tissue.
- Now damage to the endothelial tissue cause damage to platelets which results in the release of phospholipids by platelets.

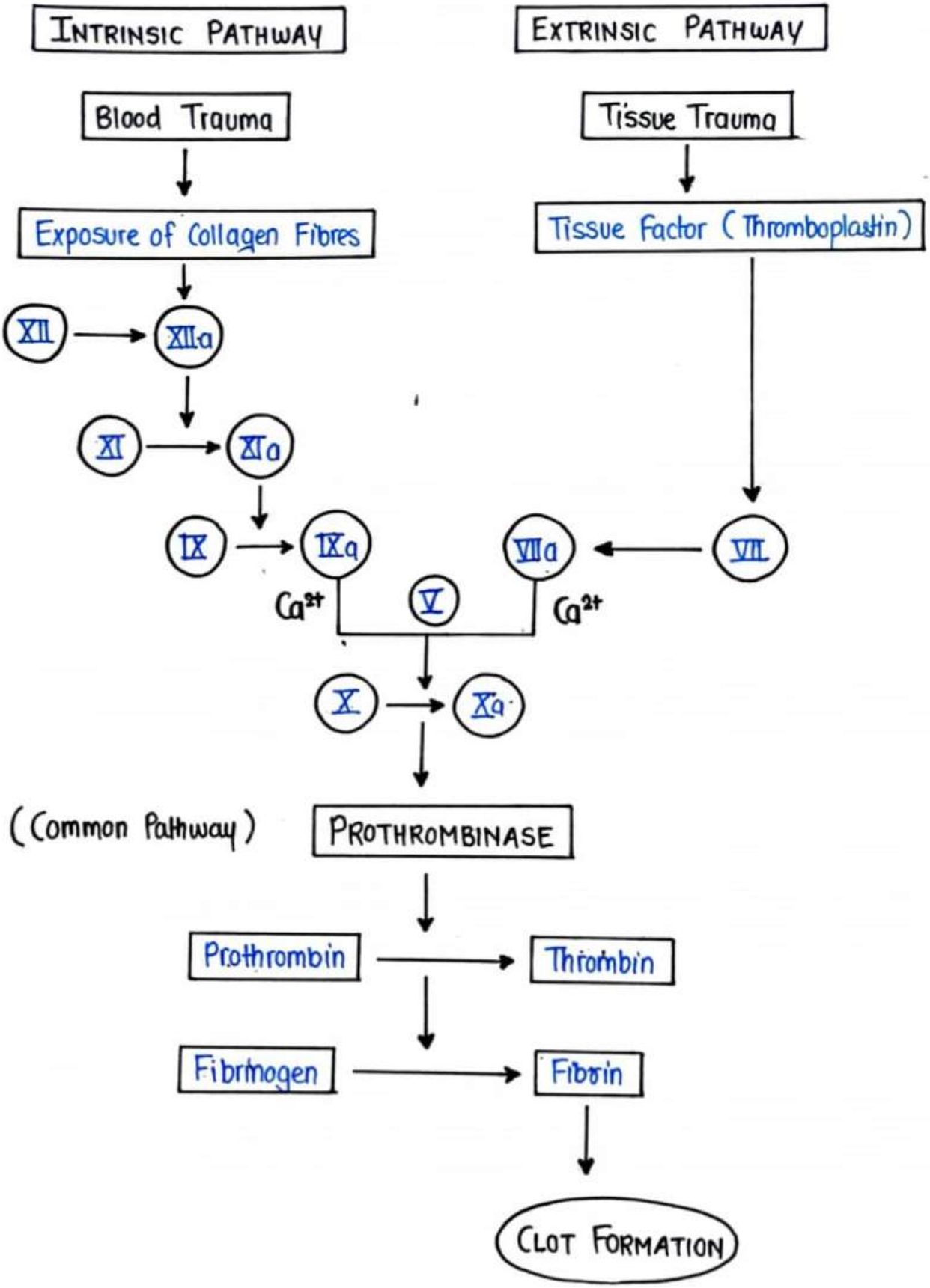
- Now all these events activates clotting factor XII which ultimately activates factor X in the presence of Ca^{2+} ions.
- Once factor X is activated, it combines with factor V & activate enzyme Prothrombinase.

Extrinsic Pathway

- It is a simple pathway & occurs rapidly
- This pathway occurs due to tissue trauma.
- In this pathway tissue factor (Thromboplastin) activates factor VII which ultimately activates factor X in the presence of Ca^{2+} ions.
- Once factor X is activated, it combines with factor V & activates enzyme Prothrombinase.

Common Pathway

- In common pathway enzyme prothrombinase converts Prothrombin into Thrombin.
- In final stage thrombin converts Fibrinogen into Fibrins in the presence of Ca^{2+} that forms clot over the damaged blood vessels.



HAEMOSTASIS

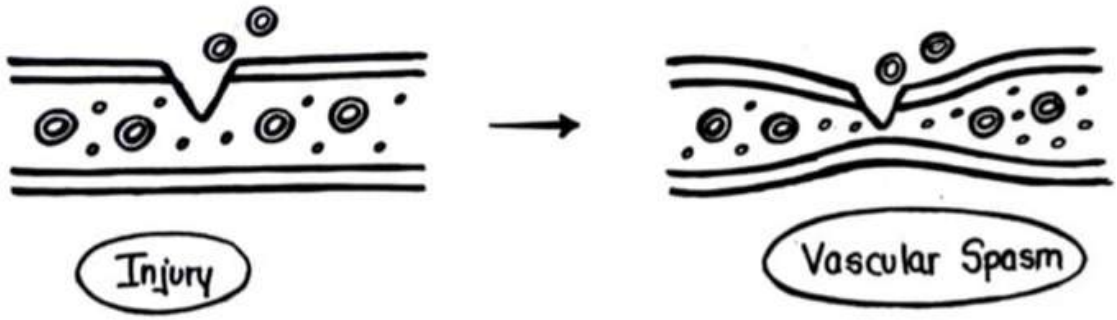
- Haemostasis is also known as 'Blood Clotting' or 'Blood Coagulation'
- It is a fast series of action for the body to stop bleeding & loss of blood.
- Haemostasis occurs when blood is present outside the blood vessel.
- Haemostasis simply stands for prevention of blood loss from a broken blood vessel.
- It requires various clotting factors and chemicals released by platelets and injured tissues.

Steps of Haemostasis

- Vascular Spasm / Vasoconstriction
- Platelets Plug formation
- Blood Clotting

Vascular Spasm

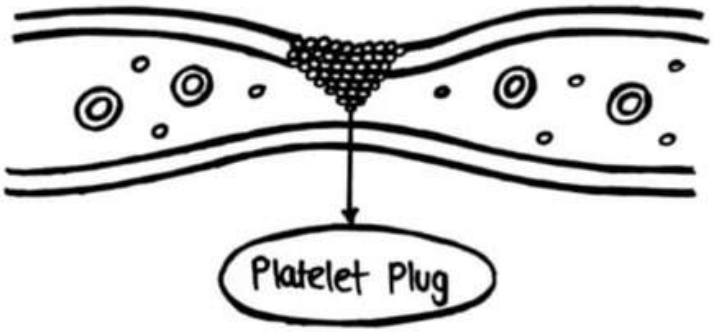
- It is also known as vasoconstriction.
- It is the blood vessel's first response towards injury.
- As the name indicates in this step blood vessel gets contracted.
- The constriction of blood vessels reduces the amount of blood & limits the blood loss.
- It is a temporary response.
- It is most effective in smaller blood vessels.



Platelet Plug Formation

- Platelets plays an important role in haemostasis process.
- In this step platelets stick together to form a plug that temporary seals the breakage in the walls of the blood vessels.
- The platelet plug formation is activated by a factor called Von Willebrand Factor (VWF)
- Platelets in the blood vessels attached with collagen fibres & become much more stickier.

- After that they release some chemical messengers such as ADP, Serotonine, Thromboxane A_2. This phase is called platelet release reaction.
- ADP cause more platelets to stick over vessels.
- Serotonine and thromboxane A_2 Enhances vascular spasm and platelet plug formation.



COAGULANTS

- Coagulants are pharmacological agents that promote the process of Blood Coagulation, which is essential for stopping bleeding.
- Coagulation is a complex physiological mechanism where liquid blood transforms into a solid clot to prevent excessive blood loss during injuries.
- Coagulants act by enhancing or initiating this process & they are used in clinical settings to manage bleeding disorders & conditions where blood clotting is impaired.

Classification Of Coagulants

They can be classified into two main categories:

① Vitamin K

- K_1 (from plants) - • Phytonadione (Phylloquinone)
- K_3 (Synthetic) - • Menadione
  • Acetomenaphthone
  • Menadione Sodium diphosphate

② Miscellaneous

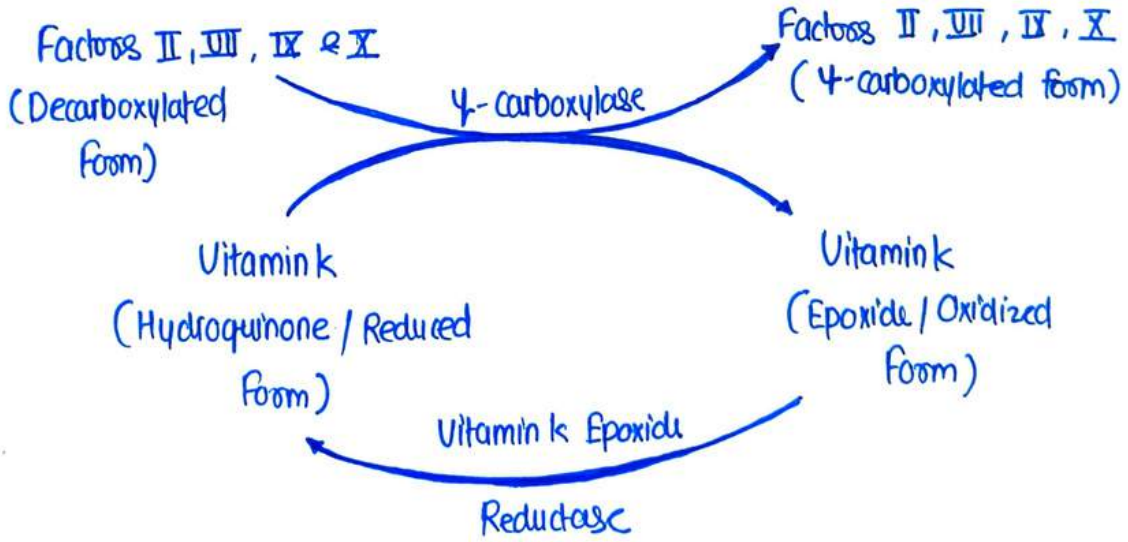
- Fibrinogen
- Antihaemophilic factor
- Desmopressin
- Adrenochrome Monosemicarbazone
- Rutin
- Ethamsylate.

Vitamin k

- Vitamin k plays a crucial role in pharmacology as a coagulant because it is essential for synthesis of certain proteins required for blood clotting.
- These proteins known as clotting factors, includes factor II, VII, IX & X as well as protein C & S which regulate clotting.

Mechanism of Action

- Vitamin k is absorbed from intestine & transported to liver
- Vitamin k is then converted to its reduced form by the enzyme Vitamin k epoxide reductase.
- Reduced vitamin k serves as a cofactor for gamma-glutamyl carboxylase which is essential for functionalization / activation of proteins like prothrombin (factor II) & factors VII, IX & X.



Therapeutic Uses

- Warfarin Overdose
- Vitamin k Deficiency
- Newborns.
- Liver disease.

Adverse Effect

- Rare but may include allergic reactions or anaphylaxis after intravenous administration.

② Other Miscallaneous Agents

- **Fibrinogen**
  - It is the soluble component of human plasma
  - On addition to thrombin, it transforms to fibrin.
  - It regulates haemorrhage related to low blood fibrinogen concentration in afibrinogenaemia or hypofibrogenaemia.

- **Antihaemophilic Factor**
  - It is a sterile freeze dried powder derived from human plasma.
  - They are particularly used in treatment of bleeding disorder mainly haemophilia A & haemophilia B.

- **Desmopressin**
  - Desmopressin is a synthetic hormone used as coagulant to treat bleeding disorders.
  - It stimulates release of factor VIII & von Willebrand factor from endothelial cells.

- **Ethamsylate**
  - Ethamsylate is a synthetic coagulant used to treat bleeding disorders.
  - It works by enhancing capillary resistance and reducing capillary permeability & increasing blood viscosity.

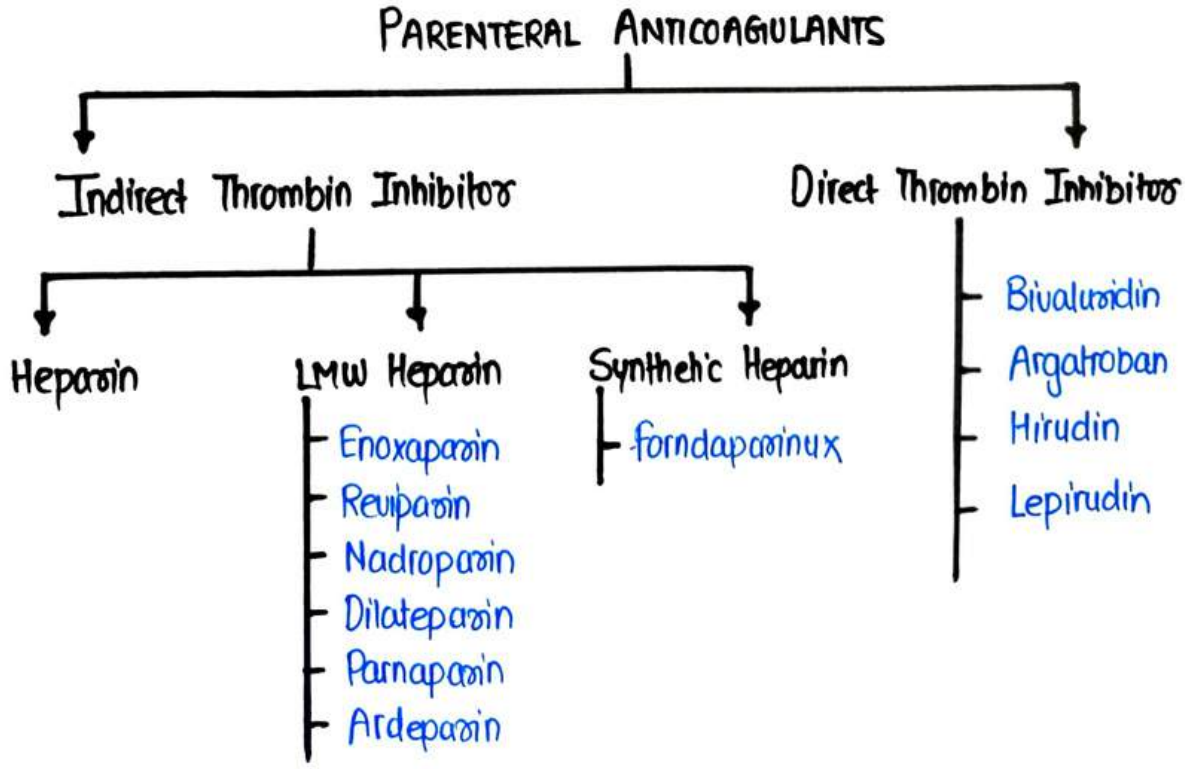
ANTICOAGULANTS

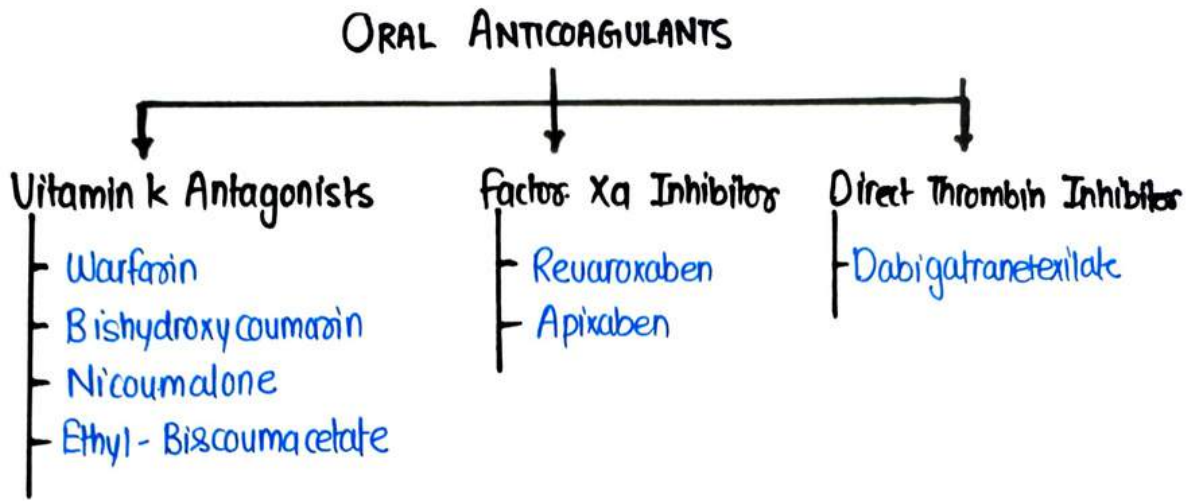
- Anticoagulants are drugs that inhibit blood coagulation, preventing the formation of harmful clots inside blood vessels.
- They are the agents that decreases coagulation ability of blood.
- They do not dissolve the already form clots, but are used to ~~formation~~ prevent the formation of new clots.

Classification Of Anticoagulants

Anticoagulants can be mainly classified into two categories.

① Parenteral Anticoagulants
② Oral Anticoagulants





① PARENTERAL ANTICOAGULANTS

- Parenteral anticoagulants are medications administered by injection to prevent or treat blood clots.
- They are commonly used in settings like Hospitals or for patients who cannot take oral medications :
- Heparin is the most commonly used Anticoagulants (Parenteral)

Indirect Thrombin Inhibitor

- Indirect thrombin inhibitors are anticoagulants that work by inhibiting thrombin through the action of antithrombin .
- It involves :

① Heparin
② Low Molecular Weight Heparins
③ Synthetic Heparin

① HEPARIN

- Heparin is most widely used anticoagulating agent.
- It was named Heparin as it was first extracted by Liver.
- It is strongest organic acid present in our body.
- It is a mucopolysaccharide found in Mast Cells of liver, lungs and intestinal mucosa.
- It does not crosses placenta thus becomes anticoagulant of choice in pregnancy.

Mechanism Of Action

- The mechanism of action of heparin as an anticoagulant primarily involves its interaction with Antithrombin III (ATIII).
- Heparin binds to Antithrombin III causing a conformational change that significantly increases its activity.
- Heparin's binding to Antithrombin allows the direct inactivation of thrombin, which is essential for converting fibrinogen to fibrin
- Antithrombin III is a natural anticoagulant in body that inactivates Thrombin (factor II) & factor X thus decreases the formation of Fibrin clots.

PHARMACOKINETICS

- **Absorption:** They a requires parenteral administration.
- **Distribution:** They rapidly distributed in bloodstream.
- **Metabolism:** They are primarily metabolised by Liver.
- **Half Life:** 1-2 hours

Therapeutic Uses

- Venous Thromboembolism
- Acute Coronary Syndrome
- Surgery / Dialysis

Adverse Effect

- Bleeding
- Osteoporosis

② LMW HEPARINS

- Low molecular weight heparins are derived from Heparin, but with smaller molecular chains
- LMWHs have lower risk of complications, however they are less potent compared to Heparin
- Like Heparin, LMWHs enhance the activity of AT III, but they have higher specificity for inhibiting ✱ Factor Xa than thrombin.
- They have longer half life & bioavailibility.
- Drugs include : Enoxaparin, Reviparin, Nadroparin, Dilateparin, Parnaparin, Ardeparin.

③ FONDAPARINUX

- Fondaparinux is a synthetic heparin & belongs to class of drugs known as factor Xa Inhibitor as it selectively inhibits factor Xa by binding to Antithrombin III..
- Used in treatment of Venous Thromboembolism & Deep Vein Thrombosis.

Parenteral Direct Thrombin Inhibitor

- Parenteral Direct Thrombin Inhibitors are class of Anticoagulant drugs that work by directly inhibiting the activity of Thrombin (Factor IIa), an enzyme crucial to the blood clotting process.
- Unlike ~~dir~~ indirect anticoagulants such as Heparin which work by enhancing the activity of Antithrombin III, DTIs bind directly to thrombin & block its ability to convert fibrinogen into fibrin, the protein that forms structural basis of a Blood Clot.

Drugs In DTIs

- Bivalirudin
- Argatroban
- Hirudin
- Lepirudin

② ORAL ANTICOAGULANTS

- These are anticoagulants taken orally & help prevent the formation of blood clots in the body.
- These drugs are often prescribed to individuals at risk of developing clots that could lead to serious conditions like
- Deep Vein Thrombosis, Pulmonary Embolism, Stroke or Heart Attacks
- They are mainly divided into 3 classes :

① Vitamin k Antagonist
② Direct Factor Xa Inhibitor
③ Oral Direct Thrombin Inhibitor

① Vitamin k Antagonist

- Vitamin k antagonist is a type of medication that inhibits the action of vitamin k, which is essential for synthesis of certain blood clotting factors.
- Warfarin is most popular oral anticoagulant.

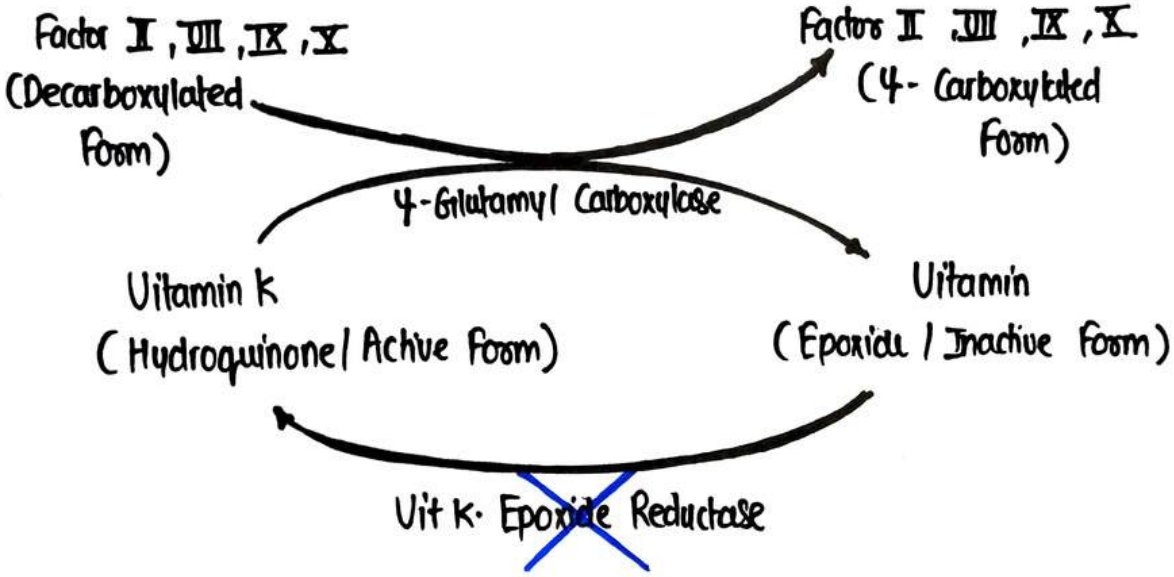
WARFARIN

- Warfarin is the most popular oral anticoagulant & used only in vivo.
- It contains 4 Hydroxycoumarine ring.
- It is a coumarin derivative & belongs to the class of Vitamin k Antagonist.

Mechanism Of Action

- Warfarin acts by inhibiting the enzyme vitamin k epoxide reductase which is necessary to recycle vitamin k into its active form.
- Active vitamin k is essential for synthesis of certain vitamin k dependent clotting factors such as

① Factor II
② Factor VII
③ Factor IX
④ Factor X



Blocked By Warfarin

Pharmacokinetics

- **Absorption :** Warfarin is well absorbed from Gastrointestinal Tract.
- **Distribution :** Warfarin is highly bound to plasma proteins, hence its highly distributed in body.
- **Metabolism :** It is primarily metabolized by liver's cytochrome P450 enzyme system.
- **Half Life :** Half Life ranges from 20- 60 hours.
- **Excretion :** Warfarin and its metabolites are excreted via urine.

Side Effects

- Bleeding
- Skin Necrosis
- Teratogenecity.

Therapeutic Uses

- Pulmonary Embolism.
- Venous Thromboembolism.

② Direct Factor Xa Inhibitors

- Factor Xa inhibitors are class of oral anticoagulants that specifically inhibit the activity of factor Xa, an essential enzyme in the coagulation that plays a key role in blood clot formation.
- By blocking factor Xa, these medications reduce the conversion of prothrombin to thrombin, leading to decreased fibrin formation & reduced clotting.

Examples

- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban

Therapeutic Uses

- Venous Thromboembolism
- Pulmonary Embolism
- Stroke Prevention

Adverse Effect

- Increased risk of bleeding, similar to other anticoagulants

③ Direct Thrombin Inhibitor

- Direct thrombin inhibitors are class of anticoagulants that directly inhibit thrombin, an enzyme crucial for conversion of fibrinogen to fibrin in coagulation process.
- By blocking thrombin, these medications prevent clot formation.

Advantages

- Rapid onset of action
- Lower risk of complications.

Adverse Effect

- Increased risk of bleeding
- Gastrointestinal issues

FIBRINOLYTICS

- Fibrinolytics, are the agents that facilitate the breakdown of fibrin, a key protein involved in blood clotting.
- These are the medications that dissolve blood clots by enhancing body's natural fibrinolytic process.

FIBRINOLYSIS

- Fibrinolysis is body's natural physiological process that breaks down fibrin, the protein that forms mesh of blood clots.
- This process is crucial for maintaining normal blood flow & preventing excessive clotting.

Mechanism Of Fibrinolysis

- Fibrinolysis begins with conversion of plasminogen into plasmin, an active enzyme
- The conversion of plasminogen into plasmin catalyses by various factors such as 'Tissue Plasminogen activator' released by endothelial cells & Urokinase found in bloodstream

Regulation

Fibrinolysis is regulated by various factors as follows:

- Plasminogen Activator Inhibitor : Inhibits tPA & Urokinase
- Alpha-2 Antiplasmin : Binds to plasmin & inhibits its activity.

Classification of Fibrinolytics

Fibrinolytics also known as Thrombolytics are mainly classified into two major categories :

① First Generation Agents

- Streptokinase
- Urokinase

② Second Generation Agents

- Alteplase
- Duteplase
- Tenecteplase
- Reteplase
- Anistreplase

① FIRST GEN FIBRINOLYTICS

- First-generation fibrinolytics refer to the earliest group of medications used to dissolve blood clots.
- These medications were developed in 1950s & 1960s and also known as plasminogen activators :
- They mainly includes :

ⓐ Streptokinase
ⓑ Urokinase

STREPTOKINASE

- It is a fibrinolytic agent used to dissolve blood clots in various thrombotic conditions :
- It is an antigen & can cause allergic reactions

Mechanism of Action

- Streptokinase activates plasminogen , converting it into plasmin that breaks down fibrin , the primary component of blood clot
- When streptokinase binds to plasminogen , it forms a complex that accelerates the conversion of plasminogen to plasmin , leading to fibrinolysis .

PHARMACOKINETICS

- Absorption : It is administered intravenously .
- Distribution : It distributed throughout the vascular system , with a significant concentration in lungs .
- Metabolism : It is primarily metabolized by liver .
- Half Life : Half Life is approx 30- 80 minutes.

Uses

- Acute myocardial infarction
- Pulmonary Embolism
- Deep Vein Thrombosis

Side Effects

- Hemorrhage , Allergic Reactions.

UROKINASE

- It is a fibrinolytic agent used primarily for the treatment of thrombotic conditions.
- It is an enzyme isolated from human urine.

MOA

Urokinase binds to surface of fibrin and plasminogen, facilitating the conversion of plasminogen into plasmin, thereby enhancing fibrinolysis.

Pharmacokinetics

- Absorption : It is administered intravenously.
- Distribution : It is distributed widely in body fluids & tissues.
- Metabolism : It is metabolized by liver & kidney.
- Half Life : 15-20 minutes

Uses

- Acute Myocardial Infarction
- Pulmonary Embolism
- Deep Vein Thrombosis

Side Effects

- Hemorrhage
- Allergic Reactions

② SECON GEN FIBRINOLYTICS

- These are the medications that dissolve blood clots and are an improvement over the frost generation.
- They were developed in 1980s & 1990s and know nas 'tissue-plasminogen activatoss'.
- They mainly include

ⓐ Alteplase
ⓑ Reteplase
ⓒ Tenecteplase
ⓓ Duteplase eh.

- These medications are similas to 1st-gen fibrinolytics but have some key differences:
- Greates fibrin specificity, reducing bleeding risk
- Longen half life
- Improved efficacy.

- They are used to treat conditions like
- Acute Myocardial Infarction
- Pulmonary Embolism
- Deep Vein Thrombosis
- Stroke eh.

ANTIPLATELET DRUGS

- Antiplatelet Drugs are medications that inhibit platelet aggregation preventing the formation of blood clots.
- They work by interfering with various pathways involved in platelet activation and aggregation.
- These drugs are commonly used to reduce the risk of cardiovascular events, such as heart attacks and strokes etc.

Mechanism Of Platelet Aggregation

- Platelet aggregation is an important step in hemostasis.
- It involves clumping together of platelets ~~plug~~ to form a platelet plug, which helps in sealing wound & initiating blood clotting.
- It involves following steps:

① Vascular Injury & Endothelial Cell Disruption

- When blood vessels are injured, endothelial cells lining the blood vessels are damaged, exposing the underlying collagen and other extracellular matrix components like **von Willebrand Factor** to the bloodstream.

② Platelet Adhesion

- Von Wibrand factor binds to exposed collagen at the site of injury.
- Platelet in the circulating blood binds to vWF via glycoprotein Ib receptors on their surface
- This allows platelets to stick to damaged site.

③ Platelet Activation

- Once adhered, platelet gets activated & release granules containing substances like ADP, Thromboxane A2, Serotonin etc.
- ADP binds to P2Y12 receptors on platelets, enhancing aggregation.
- Thromboxane A2 is a potent vasoconstrictor and platelet activator that promotes further platelet requirment & activation.

④ Platelet Aggregation

- Platelet activation leads to conformational change in Glycoprotein IIb/IIIa receptors on surface of platelets, enabling them to find fibrinogen.
- Fibrinogen acts as a bridge between Gp IIb/IIIa receptors on adjacent platelets, allowing them to stick together, forming a platelet plug.

Classification Of Antiplatelet Drugs

Antiplatelet Drugs are classified as follows :

① Thromboxane Synthesis Inhibitors

- Aspirin

② Phosphodiesterase Inhibitors

- Dipyridamole

③ P2Y12 Receptor Blocker

- Ticlopidine
- Clopidogrel
- Prasugrel
- Ticagrelor

④ Glycoprotein IIb/IIIa Receptor Inhibitors

- Tirofiban
- Eptifibatide

① Thromboxane Synthesis Inhibitor

Aspirin

Aspirin is widely used as an antiplatelet drug to prevent blood clot formation in various cardiovascular conditions such as heart attacks, strokes and other thrombotic events.

Mechanism Of Action

- Aspirin irreversibly inhibits the COX-1 enzyme in platelets.
- This inhibition prevents the conversion of Arachidonic acid to Thromboxane A2. which is a potent platelet activator and vasoconstrictor that promotes platelet aggregation by stimulating nearby platelets and inducing their adhesion to vessel wall.

Pharmacokinetics

- **Absorption** : It is rapidly absorbed from the gastrointestinal tract.
- **Distribution** : It is distributed throughout the body.
- **Metabolism** : It is metabolised by Liver.
- **Excretion** : Both aspirin & its metabolites excreted by kidneys.

Clinical Uses

- Myocardial Infarction
- Unstable Angina
- Stroke
- Deep Vein Thrombosis

Side Effects

- Gastrointestinal Effects
- Bleeding Risk
- Hypersensitivity Reactions

② PHOSPHODIESTERASE INHIBITORS

Dypyridamole

~~Dypridamole~~ Dipyridamole is an antiplatelet agent primarily used in cardiovascular diseases i.e., angina pectoris.

Mechanism Of Action

- It ~~also~~ inhibits phosphodiesterase enzymes, leading to increased intracellular levels of cyclic AMP in platelets.
- Elevated cAMP levels inhibit platelet activation and aggregation.

Pharmacokinetics

- Dipyridamole is well absorbed orally, with a peak plasma concentration occuring with 1 to 2 hours.
- It has a relatively short half-life, requiring multiple daily doses or extended-release formulations.

Clinical Uses

It's often used in combination with other antiplatelet drugs, such as aspirin, to reduce the risk of thromboembolic events, particularly in patients with a history of stroke or transient ischemic attacks.

Side Effects

Common Side Effects include headache, dizziness and gastrointestinal disturbances.

③ P2Y12 Receptor Blocker

P2Y12 receptor blockers are crucial antiplatelet medications used primarily in cardiovascular disease management.

Mechanism of Action

- P2Y12 is a g-protein coupled receptor activated by ADP.
- P2Y12 blockers prevent ADP from binding to the receptor, inhibiting platelet activation and aggregation, thus reducing the risk of thrombus formation.

Examples

- Clopidogrel
- Prasugrel
- Ticlopidine
- Ticagrelor

Clinical Uses

- Thromboembolic Prevention
- Dual Antiplatelet Therapy

Side Effects

- Bleeding Risks
- Gastrointestinal Disturbances

④ Glycoprotein IIb / IIIa Receptor Inhibitor

Glycoprotein IIb/IIIa receptor inhibitors are class of antiplatelet agents that play a crucial role in preventing platelet aggregation.

Mechanism Of Action

Glycoprotein IIb/IIIa receptors located on surface of platelets. Glycoprotein IIb/IIIa inhibitors block these receptors, preventing fibrinogen from binding and thus inhibiting platelet aggregation.

Examples

- Tirofiban
- Eptifibatide

Clinical Uses

- Acute Coronary Syndrome
- Ischemic complications.

Side Effects

- Bleeding
- Allergic Reactions.

PLASMA VOLUME EXPANDERS

- Plasma Volume Expanders are substances used to increase the volume of plasma in bloodstream that ultimately helps in restoring / maintaining the circulating blood volume in patients experiencing significant blood loss, shock, burns or dehydration.
- They are typically administered when a person's blood volume decreases to a level that compromises the cardiovascular system's ability to supply sufficient oxygen and nutrients to tissues.

Types of Plasma Volume Expanders

- There are two main types of Plasma Volume Expanders :

① Crystalloids
② Colloids

Ideal Properties

- It should have same oncotic pressure as blood.
- Its pH should between 7.35 - 7.45
- It must have rapid onset of action.
- Non toxic - Non - antigenic
- Pharmacodynamically inert
- It should be stable and inexpensive
- It should not interfering with blood grouping.

① Crystalloids

- Crystalloids are simply made up of water and electrolytes.
- They easily pass through semi-permeable membranes, means they rapidly distribute into both the intravascular and interstitial spaces
- They are less expensive and often used in initial fluid resuscitation.
- Examples :

ⓐ Normal Saline : It is 0.9% NaCl solution often used to treat dehydration and fluid loss.

ⓑ Lactated Ringer's Solution : It contains electrolytes like sodium, Potassium, Calcium and lactate often used in surgery and trauma.

ⓒ Hypertonic Saline : It is 3% saline solution used in severe hyponatremia or cerebral edema.

Therapeutic Uses

- Fluid Resuscitation
- Maintainance Therapy

Side Effects

- Fluid Overload
- Electrolyte Imbalance.

② Colloids

Colloids are solutions containing large molecules (colloidal particles) such as protein or synthetic starches that do not readily diffuse across capillary membranes.

MOA

- Colloids increases the osmotic pressure within the vascular compartment, drawing water into blood vessels and expanding plasma volume. This helps maintain circulation & improves tissue perfusion.
- They remains in the intravascular space longer than crystalloids.

Theropeutic Uses

- Hypovolemia
- Septic Shock.
- Hypoproteinemia

Side Effects

- Allergic Reactions
- Renal Impairment
- Volume Overload.

Some Most Commonly Used Colloids

① Human Albumin

- It is obtained from pooled human plasma.
- It works by increasing osmotic pressure in bloodstream.
- This causes fluid to be drawn from ~~intravascular~~ surrounding tissues into the intravascular space.
- It is mainly used in the treatment of shock, severe burns Hypoalbuminemia & Post surgery.
- It has a long lasting effect.

② Dextran

- Dextran is a type of polysaccharides that is used as plasma volume expanders in medical settings.
- They work by drawing fluid from tissues into blood vessels, helping to maintain adequate circulation & blood pressure.
- There are different molecular weight formulations of dextran, such as Dextran 40 and Dextran 70, which differ in their ability to expand plasma volume and duration of their effect.
- It is commonly used in situations like surgery, trauma or burns, where rapid restoration of blood volume is necessary.

③ Hydroxyethyl Starch

- Hydroxyethyl Starch contains more than 90% of amylopectin and has an average molecular weight of 4,50,000.
- Its effect lasts for 24-36 hours.
- Impaired kidney functions., Anaphylactic reactions and bronchospasm are major adverse effect of Hydroxyethyl Starch.

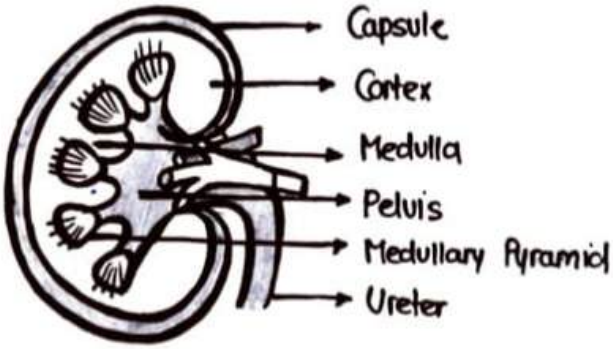
KIDNEY

- They are present in a pair in our body.
- kidneys are two bean shaped organ located on each side of vertebral column. (T-12 - L3).
- It is Reddish- brown in colour.
- It is about 10-12 cm long & 5-7 cm wide.
- Its weight is about 120-170 gram.

Layers of kidney

kidney mainly contains 3 layers:

① Outer Cortex
② Inner Medulla
③ Renal Pelvis



NEPHRONS

- Nephrons are the major functional unit of kidney.
- Nephron is mainly consist of two parts:

① Renal Corpuscle
② Renal Tubule

RENAL ~~CAPSULE~~ CORPUSCLE

- It is present in the cortex of kidney.
- The major function of renal corpuscle is filteration of blood.
- It can be further subdivided into two portions

① Glomerulus : Bunch of capillaries.
② Bowman's Capsule : Upper end of renal tubule.

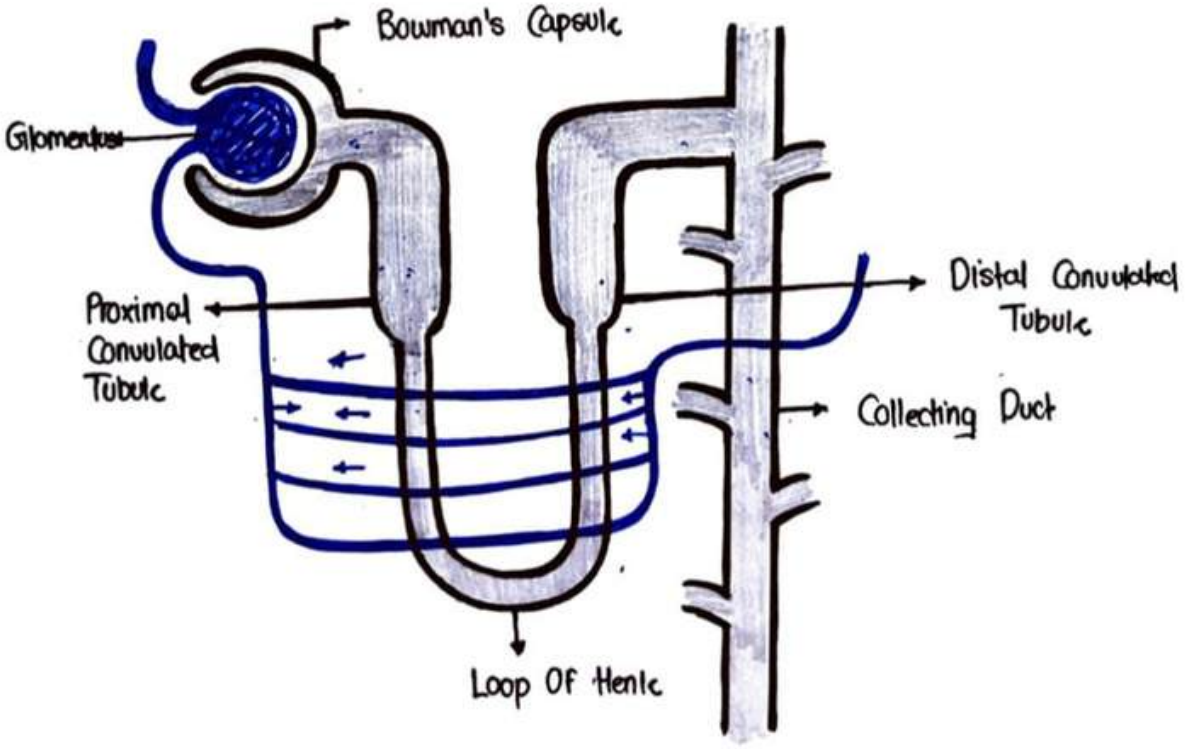
RENAL TUBULE

- It is a tube like structure and the continuation of Bowman's capsule.
- ~~Proximal~~ ∈ Renal tubule mainly consist of 3 parts :

① Proximal Convoluted Tubule : Present in Cortex
② Loop of Henle : Present in Medulla
③ Distal Convoluted Tubule : Present in Cortex

- Loop of Henle can be further subdivided into 2 parts :

(i) Descending Limb
(ii) Ascending Limb



NEPHRON

Types Of Nephrons

Nephrons are of basically two types :

① Cortical Nephrons : 85%, short Loop of Henle

② Juxta-Medullary Nephrons : 15%, Long Loop of Henle.

PHYSIOLOGY OF URINE FORMATION

- Urine formation is a Blood Cleansing function.
- Normally about 1300 ml of blood enters into the kidney.
- kidney excreted the unwanted substances from the blood as Urine.
- Normal Urine output is 1-1.5 Litre/day.

Formation Of Urine

It mainly involves 3 steps :

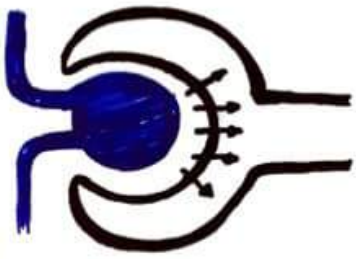
① Glomerular Filteration

② Tubular Reabsorbtion

③ Tubular Secretion

① GLOMERULAR FILTERATION

- It is a process by which blood is filtered while passing through glomerular capillaries by filteration membrane.
- It is first step of Urine formation.
- When blood passes through glomerular capillaries the plasma is filtered in bowman's capsule.



- All the substance of plasma filtered in glomerular filtrate except plasma protein & filtered fluid is known as Glomerular filterate.

Glomerular filteration Rate

- Glomerular filteration rate (GFR) is defined as total quantity of filterate formed in all the nephrons of both the kidney in the given unit of time.
- Normal GFR is 125 ml / minute or
  180 L / day

Factors Affecting GFR

- Renal blood flow
- Glomerular capillary Pressure
- Colloidal Osmotic Pressure
- Hydrostatic pressure in bowman's capsule.

② TUBULAR REABSORBTION

- As we clearly saw that about 180 L filterate formed per day but only 1.5 litre urine is excreted out from our body that means about 99% part of filterate again reabsorbed in blood.
- It is the process by which water & other necessary substances are reabsorbed from Renal Tubule to Blood.
- The reabsorbed substances moves into the interstitial fluid of renal medulla & after that they moved into ~~cap~~ tubular capillaries.
- Tubular reabsorbtion is a selective reabsorbtion as the tubular cells reabsorbs only those substances that are necessary for our body.
- Essential substances get reabsorbed while unwanted substances excreted out from body.

Site of Reabsorbtion

PROXIMAL CONVULATED TUBULE	LOOP OF HENLE	DISTAL CO. TUBULE
Glucose , Amino Acids Sodium , Potassium Calcium , Bicarbonates Chlorides , Phosphates Urea , Uric Acid Water	Sodium Chloride	Sodium Calcium Bicarbonate Water

③ TUBULAR SECRETION

- It is process in which substance are transported from blood to renal tubules.
- The unwanted substances that are not get filtered from blood to Bowman's Capsule in first step are directly transported to renal tubules later in this process.

Substance secreted in different segment of renal ~~capsu~~ tubule

- Proximal Convulated Tubule : Potassium, Ammonia, H^+ ions.
- Loop of Henle : Urea
- Distal Convulated Tubule : Potassium, H^+ ions
- Collecting Ducts : Potassium

DIURETICS

- Diuretics are the medications that increases the rate of urine flow and sodium excretion
- They are commonly used to treat conditions like high blood pressure heart failure, kidney problems and edema (swelling caused by fluid retention)
- By promoting the removal of fluid, diuretics helps to reduce the volume of blood, which can lower blood pressure & workload on heart.

CLASSIFICATION OF DIURETICS

Diuretics can be classified as follows :

① Carbonic Anhydrase Inhibitors

- Acetazolamide *
- Methazolamide
- Dichloophenamide

② Thiazides

- Chlorothiazide *
- Hydrochlorothiazide
- Hydroflumethiazide
- Cyclothiazide

③ Loop Diuretics

- Furosemide *
- Bumetanide
- Ethacrynic Acid

④ Potassium Sparing Diuretics

- Spironolactone
- Triamterene
- Amiloride

⑤ Osmotic Diuretics

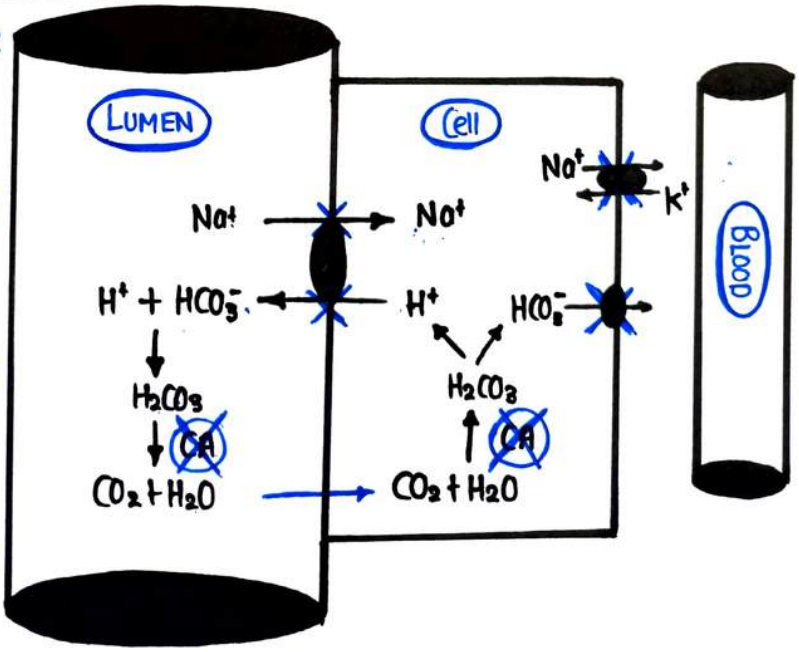
- Mannitol

① CARBONIC ANHYDRASE INHIBITORS

- Carbonic Anhydrase Inhibitors are class of diurehics that reduce the reabsorption of bicarbonate in kidneys by inhibiting the enzyme 'carbonic anhydrase'.
- These drugs give their effect on Proximal Convulated Tubule

Mechanism Of Action

Carbonic anhydrase inhibitors inhibits the carbonic anhydrase enzyme & decreases bicarbonate & sodium reabsorption thus increased excretion which leads to increased urine output



Pharmacokinetics

- Absorption : CAIs, like acetazolamide, are well absorbed orally
- Distribution : They are widely distributed in tissues, they can cross the blood brain barrier, making them effective for treating neurological conditions like certain types of seizures.
- Metabolism : These drugs are not extensively metabolized
- Excretion : They are mainly excreted by kidneys.

Therapeutic Uses

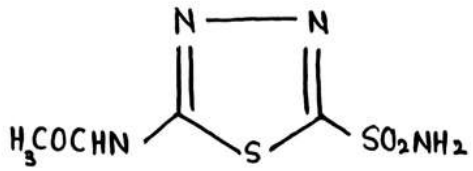
- Glaucoma
- Edema
- Epilepsy
- Metabolic Alkalosis

Adverse Effect

- Metabolic Acidosis
- Hypokalemia
- kidney Stones
- Allergic Reactions

① ACETAZOLAMIDE

Acetazolamide is a carbonic anhydrase inhibitors primarily used to treat conditions such as glaucoma, altitude sickness and certain types of epilepsy



Mechanism Of Action

- Acetazolamide is a non-competitive inhibitor of Carbonic Anhydrase.
- It inhibits CA enzyme and prevents reabsorption of bicarbonate & sodium ions thus increases urine output.

Properties

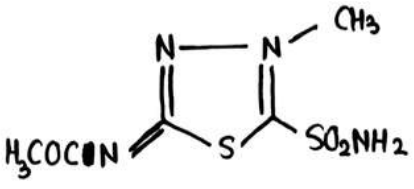
- It appears as white to yellowish crystalline powder.
- It doesn't have any odour or taste.
- It rapidly absorbed after oral administration.

Uses

- Glaucoma
- Epilepsy
- Altitude Sickness
- Edema

② Methazolamide

- It belongs to group of carbonic anhydrase inhibitors

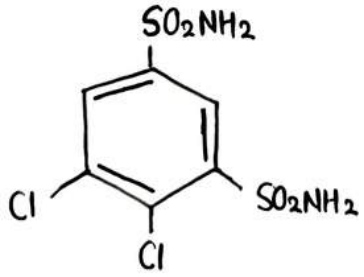


Uses

- Glaucoma
- Epilepsy
- Edema

③ Dichlorphenamide

It is a carbonic anhydrase inhibitors & commonly used as an antiglaucoma agent



Uses

- Glaucoma
- Occassional Paralysis

② THIAZIDES

- They are also known as benzothiazides, they are sulfonamide derivatives.
- These are class of drug that treat high blood pressure, edema and other conditions.

Mechanism Of Action

- Thiazides act mainly in the distal convulated tubule of nephron.
- They inhibit the sodium- chloride symporter, reducing the reabsorption of sodium and chloride.
- This leads to increased excretion of sodium, chloride and water, resulting in decreased blood volume & reduced blood pressure.

Pharmacokinetics

- Absorption : Thiazides are well absorbed orally, with peak plasma concentration occuring within 1-2 hours.
- Half Life : They typically have a half life of 6-15 hours
- Metabolism : They are minimally metabolized & primarily excreted unchanged in urine.

Uses

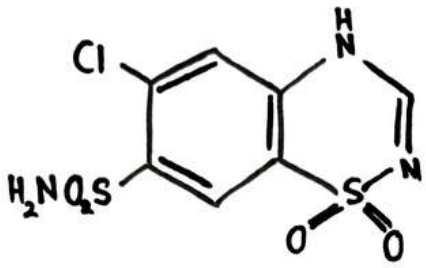
- Hypertension
- Edema
- kidney Stones

Side Effects

- Electrolyte Imbalance
- Metabolic Disorders
- Dizziness
- Headache

① CHLORTHIAZIDE *

Chlorothiazide is a thiazide diuretic often used to treat high blood pressure and fluid retention due to conditions like heart failure, liver disease & kidney disorders etc.



Mechanism Of Action

It inhibits sodium & chloride reabsorption in distal convulated tubules of the kidney result in increase excretion of sodium, chloride & water.

Properties

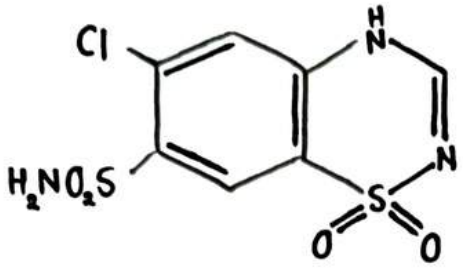
- It is a white crystalline powder
- It is slightly soluble in water & alcohol and sparingly soluble in Acetone

Uses

- Hypertension
- Edema
- Heart failure

② HYDROCHLORTHIAZIDE

Hydrochlorothiazide is a thiazide diuretic commonly used to treat high blood pressure & fluid retention

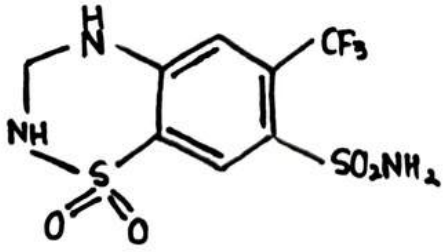


Uses

- Hypertension
- Edema
- Heart failure

③ HYDROFLUMETHIAZIDE

It is a thiazide diuretic used to treat Hypertension, edema etc.

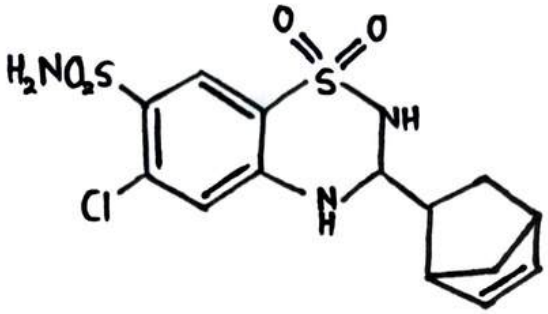


Uses

- Hypertension
- Edema
- Heart failure

⑷ CYCLOTHIAZIDE

It is a thiazide diuretic used to treat high BP & Edema.



Uses

- Hypertension
- Edema

③ LOOP DIURETICS

Loop Diurehics are class of diurehics that act on the loop of henle in the kidney to increase urine output, effectively reducing blood pressure and fluid retention.

Mechanism Of Action

- Loop Diurehics inhibit the sodium-potassium-chloride cotransporter in the thick ascending limb of loop of henle
- Inhibition of sodium-potassium-chloride transporter leads to decreased reabsorption & increased excretion, water follows excreted sodium that ultimately increases urine output

PHARMACOKINETICS

- Absorption : Most loop diuretic absorbed from GIT.
- Distribution : They are widely distributed in body.
- Metabolism : They are metabolized in liver by cytochrome P450 enzyme
- Excretion : Loop diurehics primarily excreted through kidney

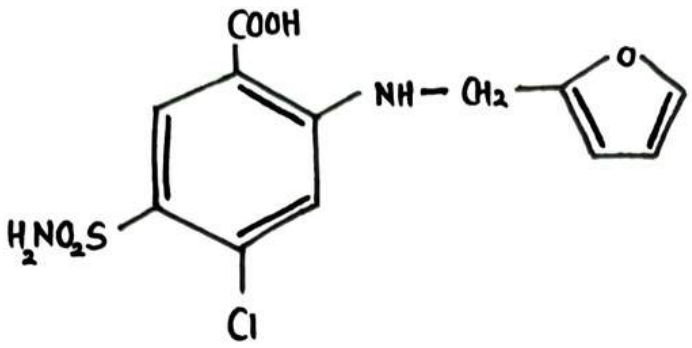
Uses

- Edema
- Hypertension
- Hypercalcemia

Side Effects

- Dehydration
- Hypotension
- Renal Impairment

① FUROSEMIDE *



Mechanism Of Action

- Furosemide works by inhibiting the sodium - potassium & chloride transporter in thick ascending loop of henle, leading to increased excretion of sodium, potassium, chloride & water.
- This reduces fluid accumulation in tissues and blood vessels.

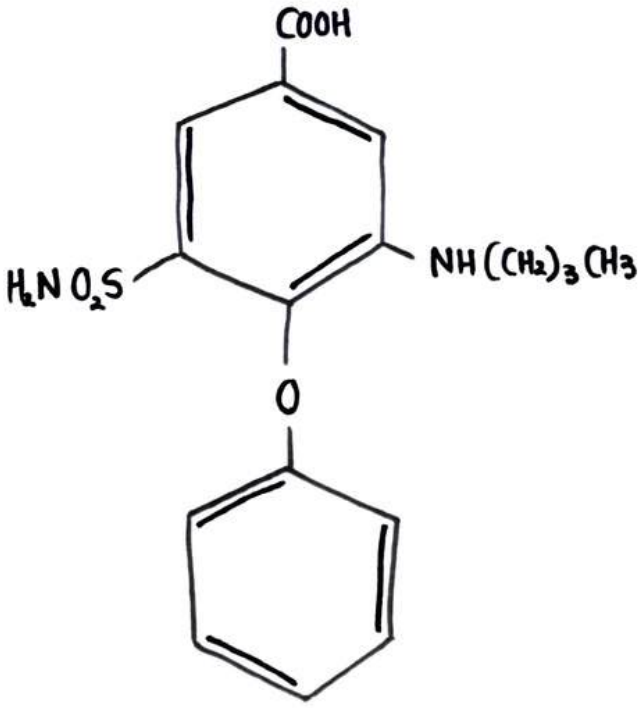
Properties

- It is a white crystalline powder.
- It is insoluble in water & soluble in acetone.

Uses

- Edema
- Congestive Heart failure
- Hypertension
- Nephrotic Syndrome

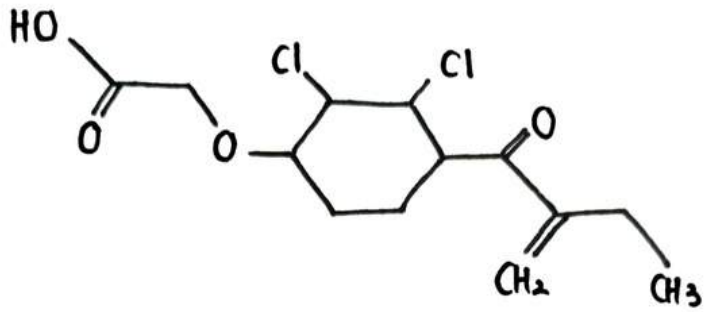
② BUMETANIDE



Uses

- Congestive Heart Failure
- Edema
- Liver Cirrhosis
- Renal Disease
- Hypertension

③ Ethacrynic Acid



Uses

- Edema
- Congestive Heart failure
- Liver Cirrhosis
- Renal Disease

④ Potassium Sparing Diuretics

Potassium sparing diuretics are class of diuretics that promotes excretion of sodium & water while decreasing excretion of potassium.

Mechanism Of Action

Mechanism of action of potassium sparing diuretics can be classified into two categories :

① Nat Channel Inhibitors : Triamterene & Amiloride
② Aldosterone Antagonist : Spironolactone

Pharmacokinetics

- Absorption : They are well absorbed orally
- Distribution : They are widely distributed throughout the body
- Metabolism : It is extensively metabolized (mainly spironolactone)
- Excretion : The drugs are excreted via urine.

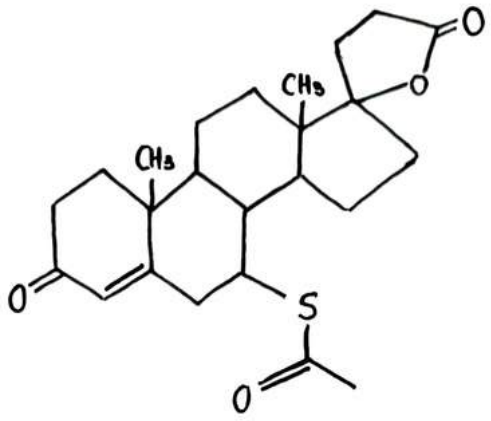
Uses

- Hypokalemia
- Hypertension
- Heart failure

Adverse Effect

- Hyperkalemia
- Gastrointestinal Disturbances

① SPIRONOLACTONE



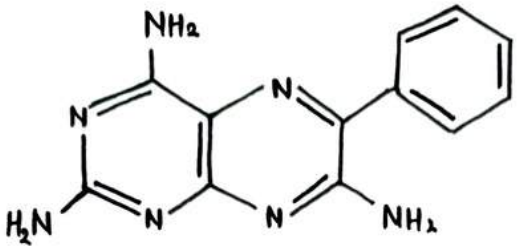
Mechanism Of Action

It is an aldosterone antagonist that blocks sodium reabsorption and potassium excretion in distal convuluted tubule.

Uses

- Hypertension
- Heart failure
- Edema
- Liver Cirrhosis

② TRIAMTERENE



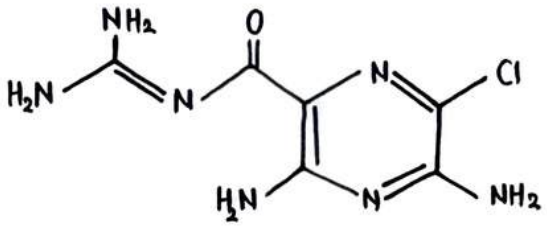
Mechanism Of Action

Inhibits epithelial sodium channels in the distal tubules, reducing sodium reabsorption and potassium excretion.

Uses

- Hypertension
- Edema
- Hypokalemia

③ AMILORIDE



Mechanism Of Action

It inhibits epithelial sodium channels in distal tubules and collecting duct, reducing sodium reabsorption & potassium excretion.

Uses

- Hypertension
- Heart failure
- Edema
- Hypokalemia

(S) Osmotic Diuretics

- Osmotic Diuretics are class of medications that promote diuresis by increasing osmolarity of blood & renal filtrate.
- The major drug used as osmotic diuretic is mannitol.

Mannitol

Mannitol is a potent osmotic diuretic commonly used in clinical settings.

Mechanism of Action

- Mannitol increases osmolarity in renal tubules, preventing reabsorption of water in kidneys.
- It draws water from cells into the bloodstream, reducing cellular edema and increasing urine output.

Pharmacokinetics

- Administration : Typically given intravenously due to poor oral absorption.
- Distribution : It rapidly distributes in extracellular space.
- Metabolism & excretion : It is not metabolized & is excreted unchanged urine.

Uses

- Cerebral Edema
- Acute kidney Injury

Side Effect

- Electrolyte Imbalance
- Dehydration

ANTIDIURETICS

- Antidiuretics are substances that reduce the production of urine by promoting water reabsorption in kidneys, helping the body to retain water
- These substances decrease the rate at which water is excreted, which can be useful in preventing dehydration or managing certain medical conditions, such as Diabetes Insipidus.

CLASSIFICATION OF ANTIDIURETICS

Antidiuretics can be classified as follows:

① Antidiuretic Hormone

- Vasopressin

② Vasopressin Analogue

- Desmopressin
- Lypressin
- Terlipressin

③ Thiazide Diuretics

- Amiloride

④ Miscalleneous

- Indomethacin
- Chlorpropamide
- Carbamazepine

① ANTIDIURETIC HORMONE

Vasopressin, also known as Antidiuretic hormone (ADH), is a peptide hormone synthesized in hypothalamus and released by posterior pituitary gland.

Mechanism Of Action

- Vasopressin acts primarily on V2 receptors located in renal collecting ducts, when vasopressin binds to these receptors, it stimulates the reabsorption of water by promoting insertion of aquaporin-2 channels into luminal membrane of renal tubule cells.
- This action increases the permeability of collecting ducts to water, allowing more water to be reabsorbed back into the bloodstream, thereby reducing urine volume.

PHARMACOKINETICS

- It is generally administered intravenously.
- It is metabolized by liver & kidneys.

Clinical Uses

- Diabetes Insipidus
- Hypotensive Emergencies
- Certain Surgeries

Side Effects

- Water Retention
- Vasoconstriction

② VASOPRESSIN ANALOGUE

- Vasopressin analogues are synthetic or modified versions of natural hormone vasopressin, designed to enhance its therapeutic properties or reduce side effects.
- These analogues primarily target the same receptors as vasopressin particularly V_1 & V_2 receptors.

Common Vasopressin Analogues

- **Desmopressin**
  - It primarily acts on V2 receptors, leading to increased water reabsorption in kidneys.
  - It is used in treatment of Diabetes Insipidus & Bedwetting.
  - It is administered intravenously, orally or intranasally & has a longer half life than vasopressin.

- **Terlipressin**
  - It acts on V1 receptors. leading to vasoconstriction & increased blood pressure
  - It is mainly used in treatment of septic shock & excessive bleeding
  - It is administered intravenously.

- **Lypressin**
  - It has similar action as vasopressin.
  - It is used in treatment of diabetes insipidus.

③ THIAZIDE DIURETICS

- Thiazide diuretics primarily promote diuresis by inhibiting sodium reabsorption in distal convulated tubule of nephron, leading to increased excretion of sodium & water.
- However, they can also exhibit an antidiuretic effect in some conditions, particularly in hypertension & Diabetes Insipidus.

Mechanism Of Action

- The exact MOA is not known. however they can show antidiuretic effect as follows.
- By inhibiting sodium & water ~~excretion~~ reabsorption & promoting their excretion, thiazides can stimulate the release of Vasopressin which promotes water reabsorption in collecting ducts.
- The mild hypovolemia stimulate the kidney to reabsorb more sodium & water in proximal tubules, decreasing the amount of water that reaches distal nephron

Clinical Uses

- Heart failure
- Hypertension
- Diabets Insipidus

THANK YOU

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