Program	**:**	**B. Pharmacy**
Semester	**:**	**V**
Subject /Course	**:**	**Pharmacology-II**
Subject/Course ID	**:**	**BP503T**
Module No.	**:**	**02**
Module Title	**:**	**Pharmacology of Drugs Acting on Cardio Vascular System**
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Learning Outcome of Module-2

LO	Learning Outcome (LO)	Course Outcome Code
LO1	Know about the introduction, definition of different cardiac vascular system diseases.	BP503.2
LO2	Know about the various types of drugs acting on CVS like therapy of shock, hematinics, coagulants and anticoagulants.	BP503.2
LO3	Know about the different classes and mechanism of action of various drugs acting on CVS.	BP503.2
LO4	Know about fibrinolytics, anti-platelet drugs and plasma volume expenders	BP503.2

Module Content Table

No.	Topic
1	Drugs used in the therapy of shock.
2	Hematinics, coagulants and anti-coagulants.
3	Fibrinolytics and anti-platelets drugs.
4	Plasma volume expanders.

2.1 DRUGS USED IN THE THERAPY OF SHOCK.

Shock is a condition in which the cardiovascular system fails to perfuse tissues adequately blood. It is due to impaired cardiac pump, circulatory system, and/or volume generalized cellular hypoxia (starvation) - widespread impairment of cellular metabolism tissue damage organ failure - death Cells switch from aerobic to anaerobic metabolism lactic acid production Cell function ceases & swells membrane becomes more permeable electrolytes & fluids seep in & out of cell Na+/K+ pump impaired mitochondria damage cell death.

Definition: Shock is defined as a state of cellular and tissue hypoxia due to reduced oxygen delivery and/or increased oxygen consumption or inadequate oxygen utilization. This most commonly occurs when there is circulatory failure manifest as hypotension (ie, reduced tissue perfusion). "Undifferentiated shock" refers to the situation where shock is recognized, but the cause is unclear. While patients often have a combination of more than one form of shock (multifactorial shock), four classes of shock are recognized.

1. Distributive
Septic shock
Systemic inflammatory response syndrome (SIRS)
Neurogenic shock
Anaphylactic shock
Drug and toxin- induced shock Septic shock
Neurogenic shock

2. Hypovolemic
Hemorrhagic
Non-hemorrhagic

3. Cardiogenic
Cardiomyopathic
Arrhythmic,

4. Obstructive
Pulmonary vascular,
Mechanical,
Combined

DRUG USED IN THE TREATMENT OF SHOCK

The following drug are frequently used for the treatment of shock such as Norepinephrine, Epinephrine, Hydrocortisone, Levophed, Methylprednisolone, Dexamethasone, Decadron, Dobutrex,

Cortef, Dexamethason intensol , Adrenacl, Medrol, Adrenalin chloride, Albumin human, Depo medrol, Isuprei Dexpak taperpak, Medrol dosepak, Phenylephrine and De-sone la

EPINEPHRINE : It stimulates both the alpha- and beta- adrenergic systems, causes systemic vasoconstriction and gastrointestinal relaxation, stimulates the heart, and dilates bronchi and cerebral vessels. It is used in asthma and cardiac failure and to delay the absorption of local anesthetics. Its pharmacological effects depend on the concentration and the type and number of available receptors; generally, it has more affinity for β receptors. So, at lower concentration, ß effect predominates. But if the number of receptors is more in an organ (e.g., blood vessels), a higher concentration of epinephrine is produced a-mediated action.

Pharmacological Action

Heart: The direct β1 receptor mediated actions of epinephrine are positive chronotropic (↑ heart rate) and ionotropic (↑ force of contraction) effect on the heart, increased cardiac output, myocadical contractility, coronary blood flow and so oxygen consumption by heart. The conduction velocity through A-V node, bundle of His, parkinje fibres, atrias and ventricular fibres is increased by epinephrine to cause the above responses. Epi → β1 recep.↑ →Gs ↑→ Ad. cycl. ↑→ CAMP ↑→PKA ↑→Ca2+-channels open [Ca2+]i ↑→ Ca^{2+} -calmodulin complex → MLCK 1 ↑ → Phosphorylation of MLC → Contraction of myocardial fibre.]

Blood Vessels: Epinephrine mainly acts on small arterioles and precapillary sphincters. It also exerts its action, to some extent, on veins and large arteries. It causes constriction of cutaneous, renal, pulmonary, arterial and venous and other visceral blood vessels because of the presence of predominant receptors. It dilates blood dilates blood vessels of skeletal muscles (at low doses), coronary and liver which is mediated by powerful B2 receptors. At higher dose, it causes vasoconstriction in skeletal muscle. [Epi - β2rec. → Gs ↑→ Ad. cycl.→ CAMP → PKA ↑ → → dephosphorylation of MLC → relaxation of VSM].

Blood Pressure: At lower concentration slow i.v infussion or S.C. injection of epinephrine causes falls in peripheral resistance because vascular B2receptors are more sensitive than α receptors. At high dose or rapid i.v. infusion produces marked increase in systolic as well as diastolic B.P (as the numbers of receptors are more than β_2 receptors in blood vessels), which is followed by a fall in the mean BP (because when the epinephrine concentration is reduced by degradation, rest of the amount remain attached on more sensitive β_2 receptors). This is called as biphasic response of epinephrine on blood pressure.

Smooth Muscle: The GIT of smooth muscle is relaxed by epinephrine. This effect is mediated by both α_1 and β_2 receptors on effectors cells and α_2 receptors on the membrane of parasympathetic nerve ending. The α_1 receptor activation causes increases in K^+ efflux and thereby hyperpolarization of the muscle cell. β_2 receptor activation increases cytosolic concentration of CAMP. Then cAMP stimulates protein kinase A which stimulates another enzyme. After 2-3 such steps this leads to dephosporylation and inactivation of myosin light chain (MLC). Stimulation of presynaptic α_2 receptors renders inhibition of release of excitatory neurotransmitter Ach from intramural nerve. These three responses combined cause relaxation of GIT smooth muscles.

Sphincter: Epinephrine usually increases sphincter contraction via α_1 receptor (by activation of phospholipase C)

Respiratory: Bronchial smooth muscle relaxes (β_2 receptors activation - cAMP↑).

Uterus: The non-pregnant uterus of human is contracted and pregnant one is relaxed by the drug. It relaxes detrusor muscle ($\beta_2$receptors) and contracts the trigone and sphincter muscles (a receptors) of the bladder.

Metabolism: It stimulates glycogenolysis (β_2 mediated) in liver and muscle, causes inhibition of insulin secretion (α mediated) and increases free fatty acids in blood (β mediated activation of triglyceride lipase breakdown of trielycerides into free fatty acids and glycerol)

Eye: Mydriasis occurs due to contraction of radial muscles (a receptors) of iris by epinephrine. The intraoccular pressure falls, especially in wide angle glaucoma, due to relaxation of ciliary muscle (B) receptors),

Skeletal Muscle: It does not directly excite skeletal muscle but facilitates neuromuscular transmission through the activation of a and Breceptors of somatic Moto neurons releasing Ach rapidly. The twitch tension of white muscle Cast contracting fibres) is increased. Whereas that of red muscle (slow fibres) is reduced. Other Bragonists (eg, salbutamol) may also act similarly.

CNS: Being polar compound, epinephrine cannot enter into the CNS but restlessness, apprehension, headache and tremor may occur due to its secondary to some peripheral effects on CNS, skeletal muscles, and intermediary metabolism.

Pharmacokinetics: Though epinephrine is absorbed from the GIT, but its bioavailability is poor because it is rapidly degraded in the intestinal wall and liver (by MAO and COMT). The absorption from im. inj. site is more rapid than s.c. inj. site, (due to local vasoconstriction).

Preparation: Adrenaline inj (BAIF, 180pg/0.1 ml). Dogs-0.1 to 0.3 ml, i.v. inj. Single-dose

vials (ImL)-25; Multi-dose vials (30mL)-1, 10

USE:

1. Cardiovascular System:

(a) Cardiac arrest adrenaline

(b) Cardiogenic shock → dobutamine, dopamine.

(c) Heart block (A-V block) isoproterenol

2. Anaphylactic reactions:

(a) Acute anaphylactic (or type I hypersensitivity) reaction Adrenaline.

3. Miscellaneous uses:

(a) Used with local anaesthetic to prolong the action adrenaline (vasoconstrictor agent)

(b) Bronchial asthma → epinephrine, isoproterenol, salbutamol

(C) As decongestant (allergic rhinitis) → epinephrine

(d) Ophthalmic use (to dilate pupil) - ephedrine, phenylephrine

NOREPINEPHRINE (LEVARTERENOL): It is also found in plants and is used pharmacologically as a sympathomimetic. It is a precursor of epinephrine that is secreted by the adrenal medulla and is a widespread central and autonomic neurotransmitter. It is the principal transmitter of most postganglionic sympathetic fibers and of the diffuse projection system in the brain arising from the locus ceruleus.

Mechanism of action: It acts on both alpha-1 and alpha-2 adrenergic receptors to cause vasoconstriction. It functions as a peripheral vasoconstrictor by acting on alpha-adrenergic receptors. It is also an inotropic stimulator of the heart and dilator of coronary arteries as a result of it's activity at the beta-adrenergic receptors.

Uses: It is mainly used to treat patients in vasodilatory shock states such as septic shock and neurogenic shock and has shown a survival benefit over dopamine. It is also used as a vasopressor medication for patients with critical hypotension.

Brand Name: Nordrin 2 mg (base)/2 ml amp, Adrenor, Norad, Vascue,

DOBUTAMINE : It is a direct-acting inotropic agent whose primary activity results from stimulation of the beta-adrenoceptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It acts primarily on beta-1 adrenergic receptors, with little effect on beta-2 or alpha receptors. It does not cause the release of endogenous norepinephrine, as does dopamine. It is indicated when parenteral B decompensation due to

depressed contractility resulting either from organic heart disease or from cardiac surgical procedures. It directly stimulates beta-1 receptors of the heart to increase myocardial contractility and stroke volume, resulting in increased cardiac output. It is proposed as a cardiotonic after myocardial infarction or open heart surgery.

Uses: It is cardiac stimulant action without evoking vasoconstriction or tachycardia. It is proposed as a cardiotonic after myocardial infarction or open heart surgery.

Brand name: Dobutamine 12.5mg/ml, Dobutamine Hydrochloride, Crdiject 50 mg/4 ml and 250 mg per 20 ml amp, Dobutrex, Dobustat 250 mg vial

HYDROCORTISONE: The main glucocorticoid secreted by the adrenal cortex. Its synthetic counterpart is used, either as an injection or topically, in the treatment of inflammation, allergy, collagen diseases, asthma, adrenocortical deficiency, shock, and some neoplastic conditions.

Mechanism of action: It binds to the cytosolic glucocorticoid receptor. After binding the receptor the newly formed receptor-ligand complex translocates itself into the cell nucleus, where it binds to many glucocorticoid response elements (GRE) in the promoter region of the target genes. The DNA bound receptor then interacts with basic transcription factors, causing the increase in expression of specific target genes.

Indications: It is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Also used to treat endocrine (hormonal) disorders (adrenal insufficiency, Addisons disease). It is also used to treat many immune and allergic disorders, such as arthritis, lupus, severe psoriasis, severe asthma, ulcerative colitis, and Crohn's disease.

Uses: Used in allergy, collagen diseases, asthma, adrenocortical deficiency, shock, and some neoplastic conditions.

METHYLPREDNISOLONE: Methylprednisolone and its derivatives, methylprednisolone sodium succinate and methylprednisolone acetate, are synthetic glucocorticoids used as anti-inflammatory or immunosuppressive agents.

Mechanism of action: Unbound glucocorticoids cross cell membranes and bind with high affinity to specific cytoplasmic receptors, modifying transcription and protein synthesis. It inhibits leukocyte infiltration at the site of inflammation, interfere with mediators of inflammatory response, and suppress humoral immune responses. The anti-inflammatory actions of corticosteroids are thought to involve phospholipase A2 inhibitory proteins, lipocortins, which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes.

DEXAMETHASONE : Dexamethasone and its derivatives, dexamethasone sodium phosphate and dexamethasone acetate, are synthetic glucocorticoids. It is used as anti- inflammatory or immunosuppressive properties and ability to penetrate the CNS. It is used alone to manage cerebral edema and with tobramycin to treat corticosteroid-responsive inflammatory ocular conditions.

Mechanism of action: It is a glucocorticoid agonist. Unbound dexamethasone crosses cell membranes and binds with high affinity to specific cytoplasmic glucocorticoid receptors. This complex binds to DNA elements (glucocorticoid response elements) which results in a modification of transcription and, hence, protein synthesis in order to achieve inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, suppression of humoral immune responses, and reduction in edema or scar tissue. The anti inflammatory actions of dexamethasone are thought to involve phospholipase Az inhibitory proteins, lipocortins, which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes.

2.2 HEMATINICS, COAGULANT AND ANTICOGULANTS

HEMATINICS

Agent that tends to stimulate blood cell formation or to increase the hemoglobin in the blood or used for the prevention and treatment of anemia.

Haemoglobin:

- Formed in red bone marrow.
- It is a conjugated protein, consisting of an iron containing pigment combined with histone (protein) is known as Globin.
- The iron containing protein is a porphyrin consisting of 4 pyrrole rings.
- This porphyrin is designated as Heam.
- Folic acid and vitamin B12 are capable of increasing the rate of Heam synthesis in the red cells.

Anemia:

- A condition in which the blood is deficient in the RBC (erythrocytes), in hemoglobin.
- Or deficiency in quality or in the quantity of blood.
- Erythrocytes are mainly responsible for the delivering oxygen to the tissues, less RBC means less oxygen to tissues.

4 types

• Microcytic anemia: Deficiency of iron (Fe).

• Macrocytic anemia: Deficiency of folic acid and B12.

• Hemolytic anemia: Abnormal breakdown of RBCs.

• Aplastic anemia: Body stops producing new blood cells. Hematinics:

IRON

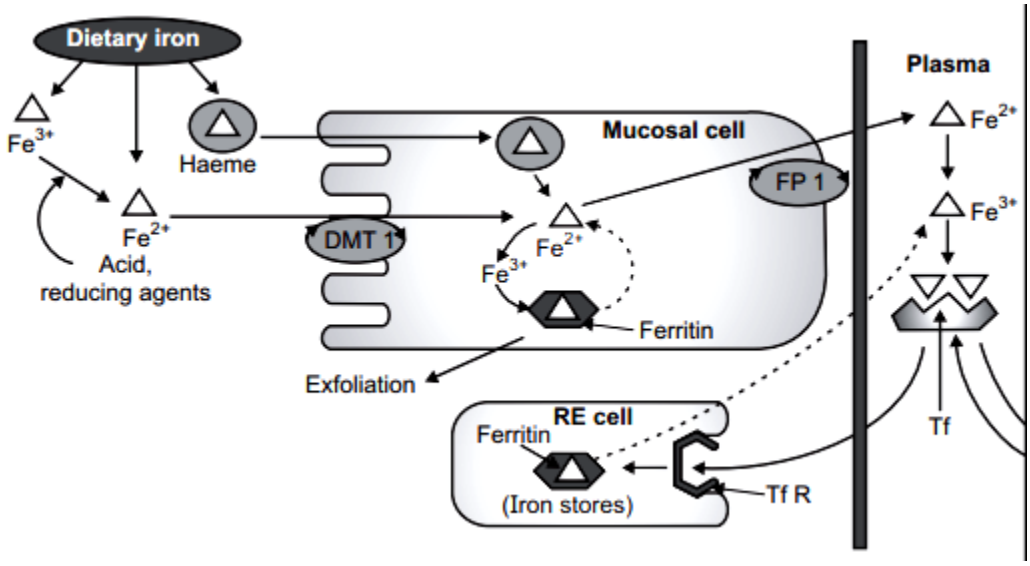
FOLIC ACID (pteroylglutamic acid). • VITAMIN B12 (cyanocobalamin)

IRON: The human body contains about 3.5 gm of iron of which about 2/3 is contained in the blood. 5 - 10% of ingested iron is absorbed. Once ingested the acid in the stomach:

1. Aids in ionization of iron
2. Splits chelated food iron from chelator
3. Maintains iron in soluble form
4. Allows iron to remain in the absorbable form Fe3+ .

Mechanism of Iron Absorption:

• Iron absorption occurs all over the intestine. • In the stomach, which contains HCL and reducing agent, convert the ferric to ferrous. • Two separate iron transporters in the intestinal mucosal cells function to effect iron absorption. • At the luminal membrane the divalent metal transporter 1 (DMT) carries ferrous iron into the mucosal cell. • The ferroportin are bound with ferrous iron and pass through mucosal cell directly into the blood steam



Transport, Utilization, Storage and Excretion:

• As such, on entering plasma it is immediately converted to the ferric form and complexed with a glycoprotein transferring (Tf).

• Iron is transported into erythropoietic and other cells through attachment of transferring receptor (Tf Rs).

• The complex is engulfed by receptor mediated endocytosis.

• Iron dissociates from the complex at the acidic pH of the intracellular vesicles.

• The released iron is utilized for haemoglobin synthesis or other purposes.

• Tf and Tf R are returned to the cell surface to carry fresh loads. Storage:

• Reticulo endothelial cells • Spleen • Bone marrow • Hepatocytes and myocytes.

Therapeutic uses of Iron:

• Iron Deficient Anemia

• Pregnancy

• Premature Babies

• Blood loss

• Hookworn infestation

• Malabsorption Syndrome

• GI Bleeding due to: o Ulcers, Aspirin, Excess consumption of coffee.

Iron Preparations:

Oral Iron:

• Ferrous Sulfate (Feosol) – 300 mg tid.

• Side Effects are extremely mild: Nausea, upper abdominal pain, constipation or diarrhea.

Parenteral

• Iron Dextran (Imferon) – IM or IV

• Indicated for patients who cannot tolerate or absorb oral iron or where oral iron is insufficient to treat the condition ie. Malabsorption syndrome, prolonged salicylate therapy, dialysis patients.

FOLIC ACID

Source in food – yeast, egg yolk, liver and leafy vegetables. Folic Acid (F.A.) is absorbed in the small intestines. F.A. is converted to tetrahydrofolate by dihydrofolate reductase. Folic Acid deficiency (F.A. Deficiency) is also called **Will's Disease.** Deficiency may produce megaloblastic anemia; neural tube defect in fetus.

Therapeutic Uses of Folic Acid

1. Megaloblastic Anemia due to inadequate dietary intake of folic acid: Can be due to chronic alcoholism, pregnancy, infancy, impaired utilization: uremia, cancer or hepatic disease.

2. To alleviate anemia that is associated with dihydrofolate reductase inhibitors: i.e. Methotrexate (Cancer chemotherapy), Pyrimethamine (Antimalarial). Administration of citrovorum factor (methylated folic acid) alleviates the anemia.

3. Ingestion of drugs that interfere with intestinal absorption and storage of folic acid: o Mechanism: Inhibition of the conjugases that break off folic acid from its food chelators. Example: Phenytoin, Progestin/estrogens (oral contraceptives)

4. Malabsorption: Sprue, Celiac disease, partial gastrectomy. 5. Rheumatoid arthritis: Increased folic acid demand or utilization. Dose: • Synthetic folic acid daily 10-30mg orally is given. Toxicity: • Non toxic to man.

VITAMIN B12:

Source:

• In food, especially in liver and kidneys. GI Microorganism synthesis, Vitamin Supplements (Cyanocobalamin).

• Necessary for normal DNA synthesis. Absorption of B12:

1. Intrinsic Factor (low dose): A protein made by stomach parietal cells that binds to B12 and delivers it from the ileum via calcium mediated event.

2. Mass Action (High dose): 1000 mg/day, absorbed via passive diffusion.

Distribution of B12:

Vitamin B12 is distributed to various cells bound to a plasma glycoprotein, Transcobalamin II.

Storage of B12:

• Excess vitamin B12 (upto 300-500 microgram) is stored in liver.

Therapeutic Uses of B12

• Daily Requirements - 0.6 - 1.0mh/day; T1/2 ~ 1 year.

• Pernicious Anemia.

• Impaired GI absorption of B12.

• Gastrectomy.

• Corrosive Injury of GI mucosa.

• Fish tape worm: worm siphons off B12.

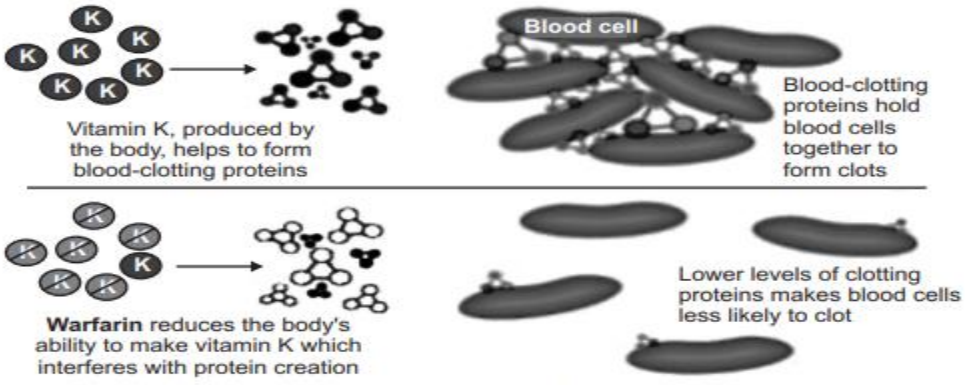
• Placebo abuse with B12, especially in elderly patients.

• Malabsorption syndrome.

COAGULANTS

Haemostasis (arrest of blood loss) and blood coagulation involve complex interactions between the injured vessels wall, platelets and coagulation factors.

Coagulants: Vitamin K : K1 (from fat-soluble): phytonadione (phylloquinone) : K3 (synthetic) • Fat soluble (Menadione, Acetomenaphthone) • Water soluble (Menadione sod. Bisulfite, Menadione sod. Diphosphate. • Miscellaneous: Fibrinogen (human), Antihaemophilic factors, Desmopressin, Adrenochrome monosemicarbazone, Rutin, Ethamsylate. Vitamin K: • Vit. K is a fat-soluble dietary principle required for the synthesis of clotting factors. • Daily requirements: Vit. K2 produced by colonic bacteria and 3-10 µg/day external source may be sufficient. The total requirement of Vit. K for an adult has been estimated to be 50-100 µg/day. Mechanism of Action: • Vit. K acts as a cofactor at a late stage in the synthesis by liver of coagulation proteins – prothrombin, factors VII, IX and X.



Uses:

The only use of Vitamin K is in prophylaxis and treatment of bleeding due to deficiency of clotting factors.

Plasma Fractions:

• Deficiencies in plasma coagulation factors can cause bleeding.

• Factor VIII deficiency (classic hemophilia or hemophilia A) and factor IX deficiency (Christmas disease, or hemophilia B) account for most of the heritable coagulation defects. Concentrated plasma fractions and recombinant protein preparations are available for the treatment of these deficiencies.

Desmopressin Acetate:

• Desmopressin (DDAVP) stimulates the release of von willebrand factor (Vwf) from the Weibel-palade bodies of endothelial cells; thereby increasing the levels of Vwf (as well as coagulant factor VIII) 3 to 5 fold.

• It is also used to promote the release of Vwf in patients with coagulation disorders such as von willebrand disease, mild hemophilia A and thrombocytopenia. Cryoprecipitate:

• It is a plasmaprotein fraction obtainable from whole blood. It is used to treat deficiencies or qualitative abnormalities of fibrinogen.

• It may also be used for patients with factor VIII deficiency and Willbrand disease.

ANTICOAGULANT

Drugs that prevent blood coagulation and stop the occurrence or expansion of a thrombus.

Classification:

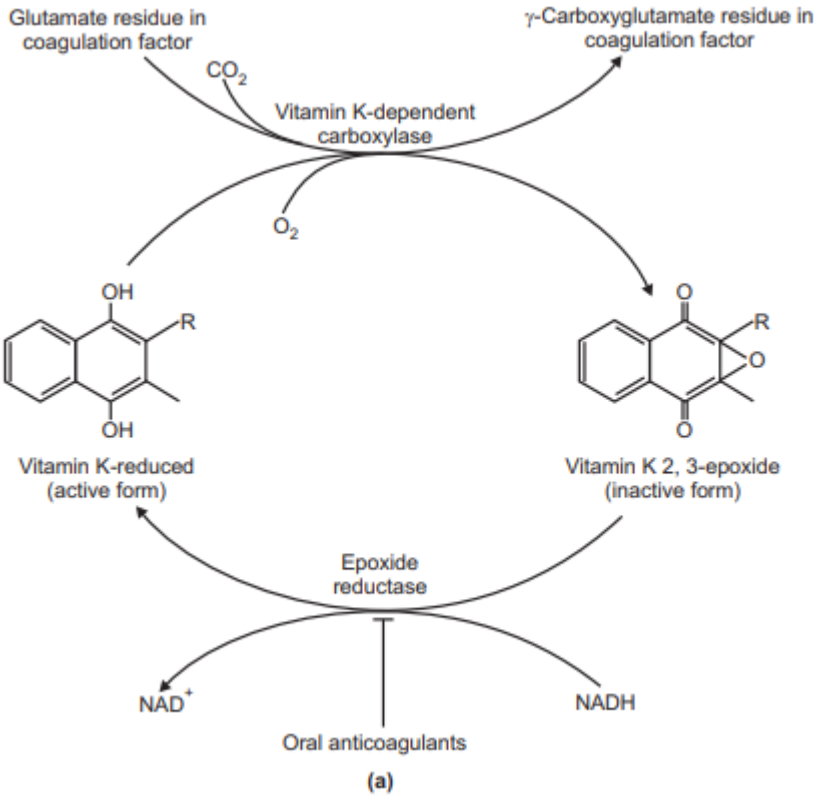
1. Vitamin K antagonist - Warfarin.

2. Heparin and related drugs: (a) Heparin. (b) LMWH (Enoxaparin, Dalteparin, Tinzaparin). (c) Synthetic heparin derivatives (Fondaparinux – longer acting).

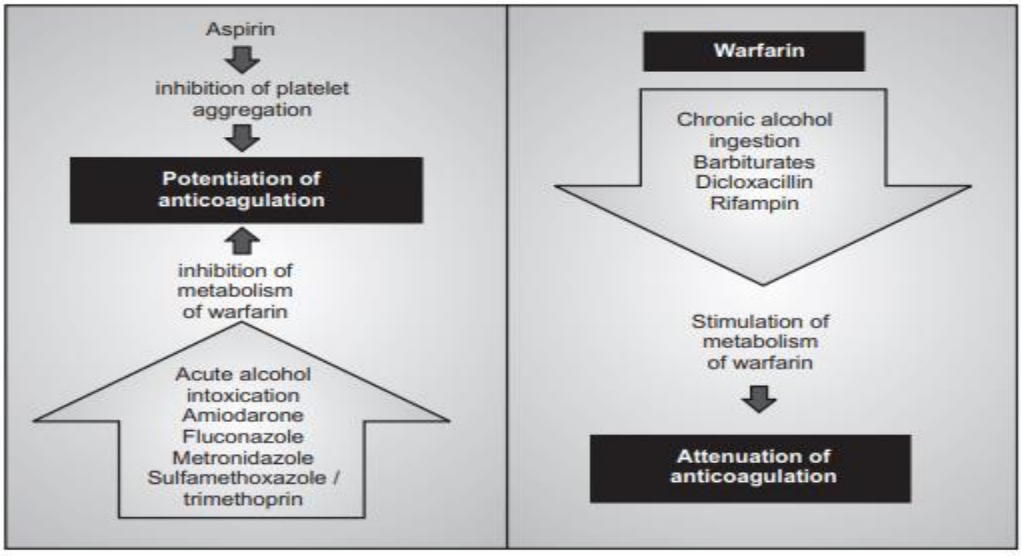
3. Direct thrombin inhibitors: (a) Parenteral → Hirudin, Lepirudin, Argatroban, Bivalirudin. (b) Oral → Dabigatran.

4. Active factor Xa inhibitor → Rivaroxaban, Apixaban. Warfarin:

• Competitively inhibits vitamin K epoxide reductase and inhibits the post-translational carboxylation of glutamate residues on vitamin K dependent coagulation factors II (prothrombin), VII, IX, and X.



(a)



Heparin:

• Antithrombin III-Irreversibly inactivates thrombin and factor Xa.

• Heparin potentiates anti-thrombin III activity. Advantages of LMWH:

1. Can be administered s.c.

2. Effects are consistent and dosing less frequent (Long t1/2 and elimin. By 1st order kinetics).

3. Dose is given in mg (not in units) can be easily calculated on body weight basis.

4. Chance of haemorrhage is less.

5. Risk of osteoporosis is decreased.

	Heparin	Warfarin
Route of administration	I.v., S.c.	Oral
Onset of action	Immediate	Delayed
Mechanism	Activ. Of AT-III	Decrease activ. Of c.f. 2,7,9,10
Antagonist	Protamine sulphate	Vitamin K
Use	To initiate therapy	For maintenance

Uses of anti-coagulants:

1. Myocardial infarction
2. Unstable angina
3. Rheumatic heart disease
4. Cerebrovascular disease
5. Haemodialysis
6. Defibrination syndrome (DIC).

FIBRINOLYTICS AND ANTI-PLATELETS DRUGS

FIBRINOLYTIC SYSTEM

- The process of dissolution of clot is called fibrinolysis.

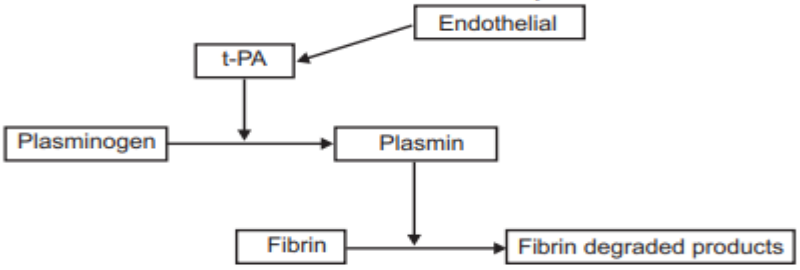
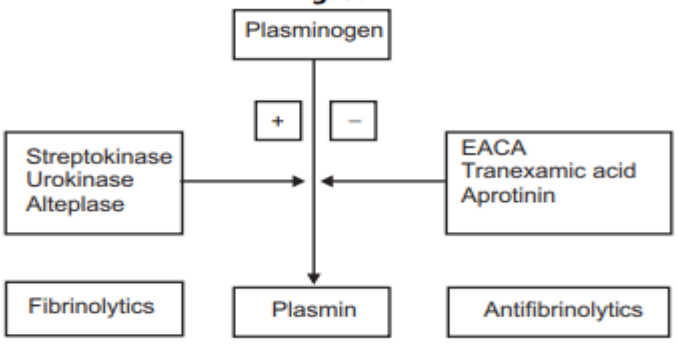


Fig. 9.1



FIBRINOLYTICS

• Used to lyse the thrombi / clot to re-channelize the occluded blood vessel (mainly coronary artery).

• Work by activating the Fibrinolytic system:

STREPTOKINASE

UROKINASE

RETEPLASE (analogue of alteplase)

ALTEPLASE (tissue - Plasminogen Activator [t-PA])

TENECTEPLASE Streptokinase:

• Obtained from - hemolytic streptococci.

• Binds with circulating plasminogen to form plasmin.

• Complex that activates plasminogen to plasmin.

• t½ = 30 − 80 min.

• Antigenic, Pyrogenic.

• Destroyed by circulating antistreptococcal antibodies.

• Hypotension and Arrhythmia can occur

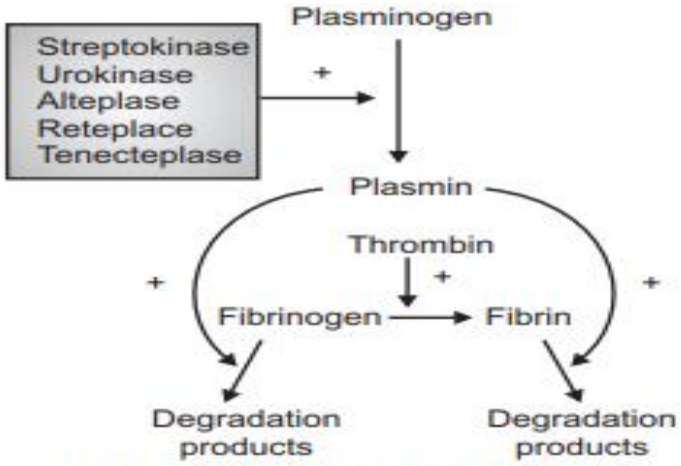


Fig. 9.3: MoA of Fibrinolytics

Uses:

• Acute myocardial infarction, – 7.5 to 15 lac IU; I.V over 1 hr period.

• Deep vein thrombosis, pulmonary embolism.

Adverse Effects:

• Bleeding, hypotension, allergic reactions, fever, arrhythmias. Contraindications:

• Recent trauma, surgery, abortion, stroke, severe.

• hypertension, peptic ulcer, bleeding disorders.

Urokinase:

• Enzyme isolated from human urine, now prepared from cultured human kidney cells.

• Direct plasminogen activator.

• t ½ of 10 to 15 min. • Non-antigenic, Non-allergenic.

• Fever can occur but hypotension rare.

• Indicated in patients in whom streptokinase has been for an earlier episode.

Alteplase:

• Recombinant tissue Plasminogen Activator (rt-PA)

• Selectively activates plasminogen bound to fibrin

• Non-antigenic, not destroyed by antibodies

• Rapid acting, more potent

• Superior in dissolving old clots

• Short half life 4-8 min

• Nausea, mild hypotension, fever may occur

• Expensive.

Newer Recombinant Tissue Plasminogen Activators:

• Reteplase:

Modified rt-PA.

Longer half life 15 -20 min, but less specific for fibrin bound plasminogen.

Tenecteplase:

Genetically engineered mutant form of alteplase.

Higher fibrin selectivity and longer half life – 2 hrs.

Single bolus dose 0.5 mg/kg sufficient. Very expensive.

Uses of Fibrinolytics:

• Acute myocardial infarction.

• Deep vein thrombosis.

• Pulmonary embolism.

• Peripheral arterial occlusion.

• Ischemic Stroke.

ANTIPLATELET DRUGS

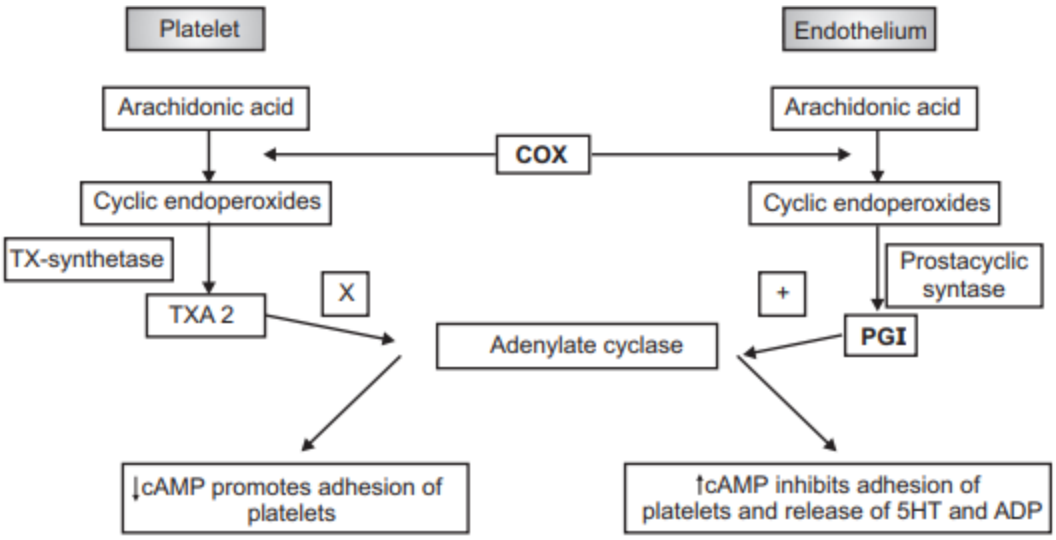
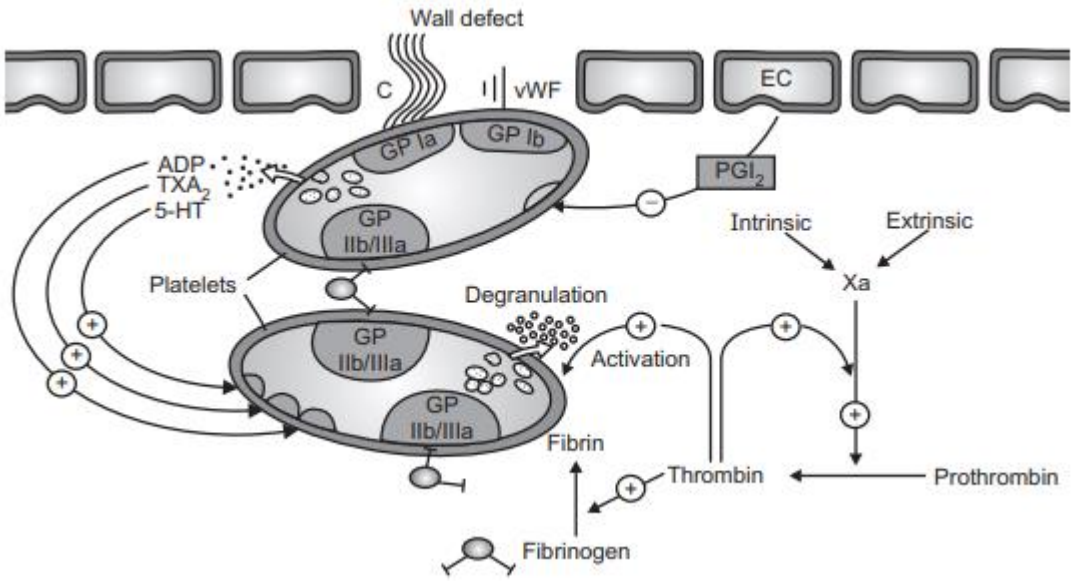


Fig. 9.4: Mechanism of Platelet Aggregation and Inhibition



Antiplatelet Drugs (Classification):

• TXA2 synthesis inhibitor:

Low dose aspirin

• Phosphodiesterase inhibitor:

Dipyridamole, cilostazole

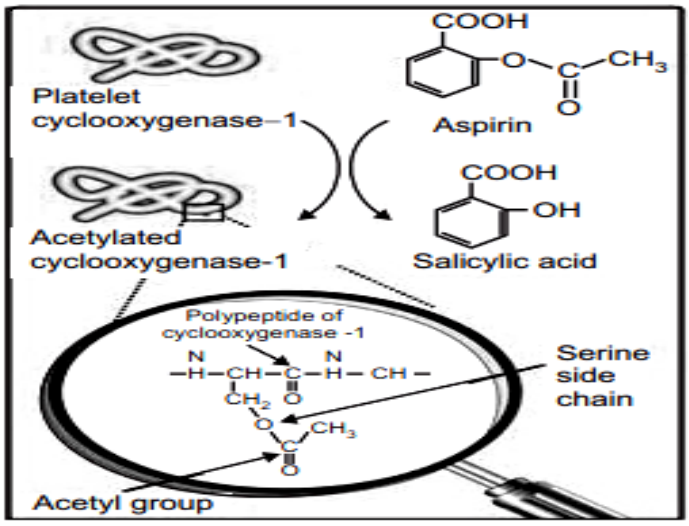
• Thienopyridine derivatives (ADP antagonists):

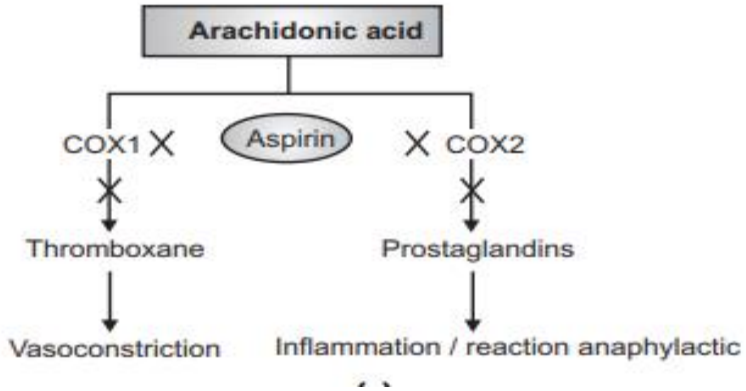
Ticlodipine, clopidogrel

• Gp-IIb/IIIa receptor antagonists o Abciximab, eptifibatide, tirofiban

• Others o PGI2, daltroban, dazoxiben, clofibrate

Aspirin:





Dipyridamole:

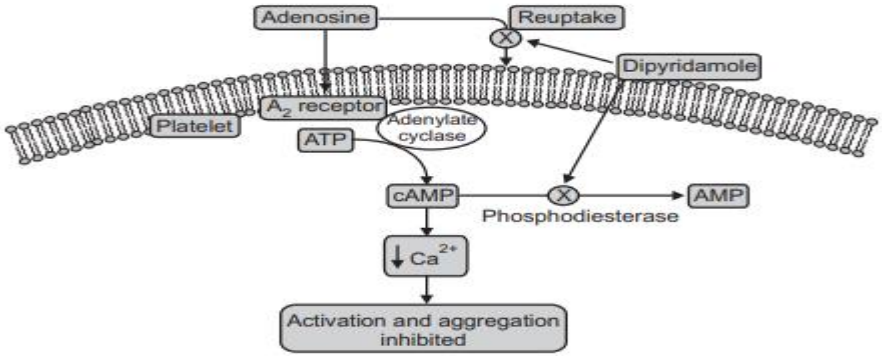
• Coronary vasodilator and relatively weak antiplatelet drug.

Mechanism of Action:

• Potentiates effect of endogenous prostacycline.

• In high concentration inhibits Phosphodiesterase, so increase cAMP. Dose = 100 mg BD/TDS.

Used with aspirin to prevent ischemic stroke in patients of TIA.



Ticlodipine and Clopidogrel:

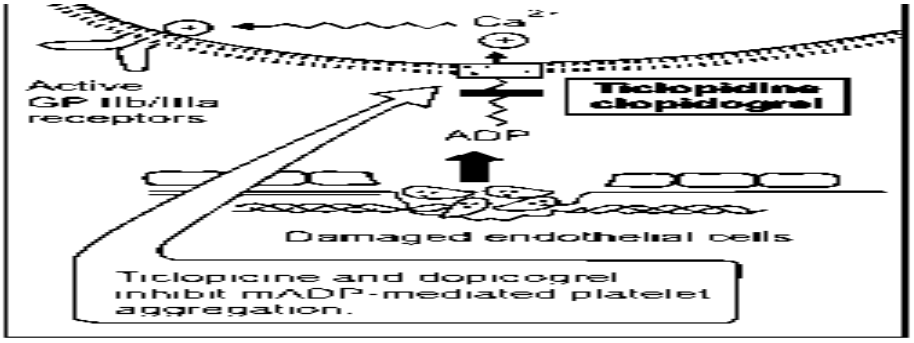
• ADP antagonists, inhibit binding of ADP to its receptors irreversibly.

• Also Inhibit fibrinogen induced platelet aggregation without modifying GPIIb/IIIa.

• Synergistic action with aspirin.

• Both are prodrugs have long duration of antiplatelet effect.

• Clopidogrel a congener of ticlodipine is safer and better tolerated.



Ticlodipine:

• Adverse effects:

Diarrrhoea, vomiting, abdominal pain o Headache, tinnitus, skin rash o Bleeding, neutropenia, thrombocytopenia

• Dose = 250 mg BD.

Clopidogrel:

• Adverse effects: Bleeding most IMP

Less bone marrow toxicity

Diarrhoea, epigastric pain, rashes

• Dose = 75 mg OD.

Abciximab:

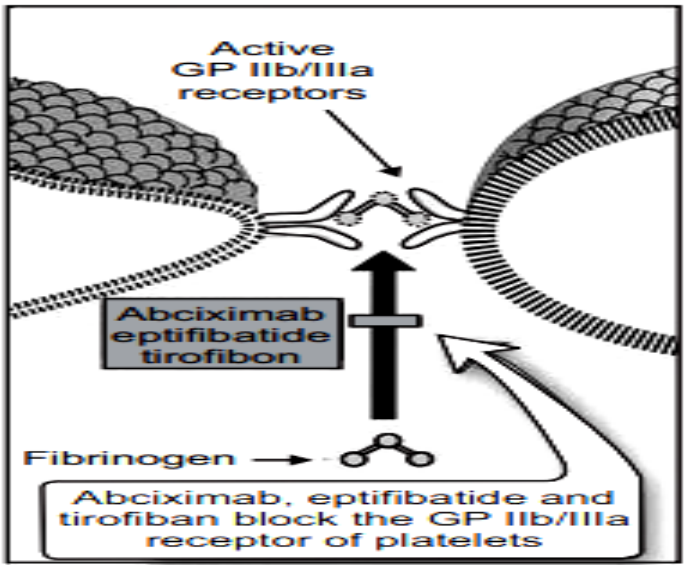
• Fab fragment of Chimeric monoclonal antibody against GP-IIb/IIIa.

• Used to prevent platelet aggregation in patients having PCI, administered along with aspirin & heparin or LMW heparin.

• Most common A/E is bleeding.

• May cause thrombocytopenia, hypotension, bradycardia.

• Non antigenic.



Uses of Antiplatelet Drugs:

• Prosthetic heart valves & A-V shunts

• Peripheral vascular disease

• Coronary artery diseases

Myocardial infarction

Unstable angina o Primary & secondary prevention of MI

• Coronary angioplasty, stents, bypasses implants

• Cerebrovascular transient ischemic attacks

• Venous thrombo-embolism.

PLASMA VOLUME EXPANDERS

Blood: Is a fluid connective tissue that circulates continuously around the body, allowing constant communication between tissues distant from each other. Plasma: Plasma is a clear, straw colored, watery fluid in which several different types of blood cells are suspended.

• Plasma expanders are agents that have relatively high molecular weight and boost the plasma volume by increasing the osmotic pressure.

• They are used to treat patients who have suffered hemorrhage or shock.

• Volume expanders are the intravenous fluid solutions that are used to increase or retain the volume of fluid in the circulating blood.

• Generally volume expanders are used to replace fluids that are lost due to illness, trauma or surgery.

• These are used to correct hypovolemia due to loss of plasma or blood.

TYPES OF VOLUME EXPANDERS

• There are two main types of volume expanders:

1. Crystalloids: Crystalloids are aqueous solutions of mineral salts or other watersoluble molecules. E.g. normal saline, dextrose, Ringer's solution etc.

2. Colloids: Colloids are larger insoluble molecules, such as dextran, human albumin, gelatin, blood. Blood itself is a colloid.

• The larger molecules of colloids are retained more easily in the intravascular space & increase osmotic pressure. So, more effective resuscitation of plasma volume occurs by colloids than produced by that of crystalloids.

• Duration of action of colloid relatively longer than crystalloid. Colloid:

• Increase plasma volume.

• Less peripheral edema.

• Smaller volume for resuscitation.

• Intravascular half life 3-6 hrs.

Crystalloid:

• Inexpensive.

• Use for maintenance of fluid and initial resuscitation.

• Intravascular half life 20-30 minutes. Ideal properties of PVEs (Plasma Volume Expanders):

• Iso-oncotic with plasma.

• Distributed to intravascular compartment only.

• Pharmacodynamically inert.

• Non-pyrogenic, non-allergenic & non-antigenic.

• No interference with blood grouping or cross-matching.

• Stable, easily sterilizable and cheap.

Generally used Plasma Expanders:

• Human albumin.

• Dextran.

• Degraded gelatin polymer (Polygeline).

• Hydroxyethyl starch (Hetastarch/HES).

• Polyvinyl pyrrolidone –PVP.

Mechanism of Action:

• Generally works on the principle of osmosis.

• Increases plasma osmotic pressure, drawing water into plasma from interstitial fluid.

• Since the lost blood is replaced with a suitable fluid, now the diluted blood flows more easily, even in small vessels.

• As a result of chemical changes, more oxygen is released to the tissues. Uses of Plasma Expanders:

• Used in conditions where blood or plasma has been lost or has moved to extravascular compartments e.g., in burns, hypovolaemic shock, endotoxin shock, severe trauma and extensive tissue damage.

• Can also be used as a temporary measure in cases of whole blood loss till the same can be arranged.

Note: They do not have oxygen carrying capacity.

1. **Human Albumin:**
   - It is obtained from pooled human plasma.
   - It can be used without regard to patient's blood group and doesn't interfere with coagulation.
   - It is free of risk of transmission of hepatitis because the preparation is heat treated.
   - Crystalloid solution must be infused concurrently for optimum benefit.
   - It has been used in acute hypoproteinaemia, acute liver failure and dialysis.
   - It is comparatively expensive.
   - Available products: o Albudac, Albupan 50, 100 ml inj., o Albumed 5%, 20% infusion (100 ml)
2. **Dextran:**
   - It is highly branched polysaccharide molecule obtained from sugar beat.
   - It is produced by using the bacterial enzyme dextran sucrase from the bacterium Leuconostoc mesenteroides which grows in a sucrose medium.

• Most commonly used plasma expanders and is available in two forms.

1. Dextran 70 2. Dextran 40

(a) Dextran 70: 1. It is most commonly used preparation.

2. It expands plasma volume for nearly 24 hrs.

3. Excreted slowly by glomerular filtration as well as oxidized in body over weeks.

4. Some amount is deposited in retuculoendothelial cells. Dextran 70 has nearly all the properties of ideal plasma except:

• It may interfere with blood grouping and cross matching.

• It can interfere with coagulation and platelet function and thus prolong bleeding time.

• Some polysaccharide reacting antibodies, if present, may cross react with dextran and trigger anaphylactic reaction like Urticaria, itching, bronchospasm, fall in BP.

(b) Dextran 40:

• It is 10% solution in Dextrose or Saline.

• It acts more rapidly than dextrose - 70.

• It reduces blood viscosity.

• It is excreted through renal tubules and occasionally may produce acute renal failure.

• The total dose should not exceed 20 ml/kg in 24 hr.

• Dextrans can be stored for 10 years and are cheap so are the most commonly used plasma expanders.

Caution: Dextran doesn't provide necessary electrolytes and can cause hyponatremia or other electrolyte disturbances.

3. Degraded Gelatin Polymer (Polygeline);

• It is synthetic polymer (polypeptide) of MW-30,000.

• It doesn't interfere with blood grouping and cross matching and is non-antigenic.

• Expands plasma volume for 12 hrs.

• It is more expensive than dextran and can also be used for priming of heart-lung and dialysis machines.

Brands:

Haemaccel; Seraccel 500 ml vaccine.

4. Hydroxyethyl starch(Hetastarch)

• It is a complex mixture of ethoxylated amylopectin of various molecular sizes; average MW 4.5 lacs.

• It maintains blood volume longer.

• It doesn't cause acute renal failure or coagulation disturbances.

• It improves hemodynamic status for 24 hrs.

Adverse effects:

• Vomiting, mild fever, itching, chills, flu like symptoms, swelling of salivary glands, Urticaria, bronchospasm etc.

Brand:

• Expan 6% inj. (100 , 500 ml vac).

• It has also been used to improve harvesting of granulocytes because it accelerates erythrocyte sedimentation.

Adverse effects:

• Anaphylactic reactions, mild fever, chilling, periorbital edema, Urticaria, itching.

5. Polyvinylpyrrolidine(PVP)

• It is a synthetic polymer of average MW 40,000 used as a 3.5% solution.

• PVP was used as blood plasma expander for trauma victims after the 1950s.

• It interferes with blood grouping and cross matching and is histmine releaser.

• It binds to penicillin and Insulin.

• It is excreted by kidney and small amounts by liver into bile.

• A fraction is stored in RE cells for prolonged periods.

• It is less commonly used plasma expander.

Uses of PVP:

• PVP is also used in personal care products such as shampoos and toothpaste, hair sprays and gels.

• It is used as binder in many pharmaceutical tablets.

• PVP added to Iodine forms a complex called Povidone- Iodine that posses disinfectant properties. And known under the trade name of Betadine and Pyodine.

Some Crystalloids:

1. Normal Saline (Isotonic):

• It is the crystalloid fluid containing 0.9% NaCl.

• The pH of isotonic saline is considerably lower than the plasma pH.

• NS is frequently used in patients who cannot take fluids orally and have developed dehydration or hypovolemia.

2. Lactated Ringer's solution:

• It was introduced in 1880 by Sydney ringer, a British physician.

• The solution was designed to promote the contraction of frog hearts and was contained with calcium and potassium in a NaCl diluents .

• It is contraindicated as diluents for blood transfusions.

3. Dextrose solutions:

• Generally 5% dextrose solutions are used which provides 170 kcal/lit.

• It is IV sugar solution which provides some energy to the body parts.

• Osmolarity is lower than serum.

• Useful when kidney function is impaired.

Contraindications to Plasma Expanders:

• Allergy

• Heart failure

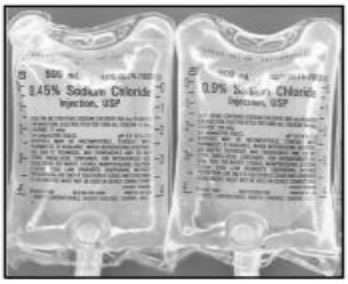
• Severe anaemia

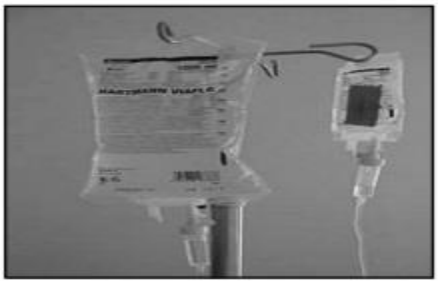
• Thrombocytopenia

• Pulmonary edema

• Renal insufficiency.

Some commercially used Plasma volume expanders:





PHARMACOLOGY OF DRUGS ACTING ON URINARY SYSTEM

Diuretics are the materials that promote the excretion of urine.

• Promotes the excretion of the (Na^+), (Cl^-) or (HCO_3^-) and water.

• Net result being:

- ✓ Increase the urine flow.
- ✓ Change urine pH.
- ✓ Change the ionic composition of the urine and blood.

• Diuretics are very effective in the treatment of edema, CHF, pregnancy and nutritional nephrotic syndrome, hypertension, cirrhosis of liver and also lower the intracellular and CSF pressure.

Normal Physiology of Urine Formation

• **Kidney:** 1.3 million nephron each.

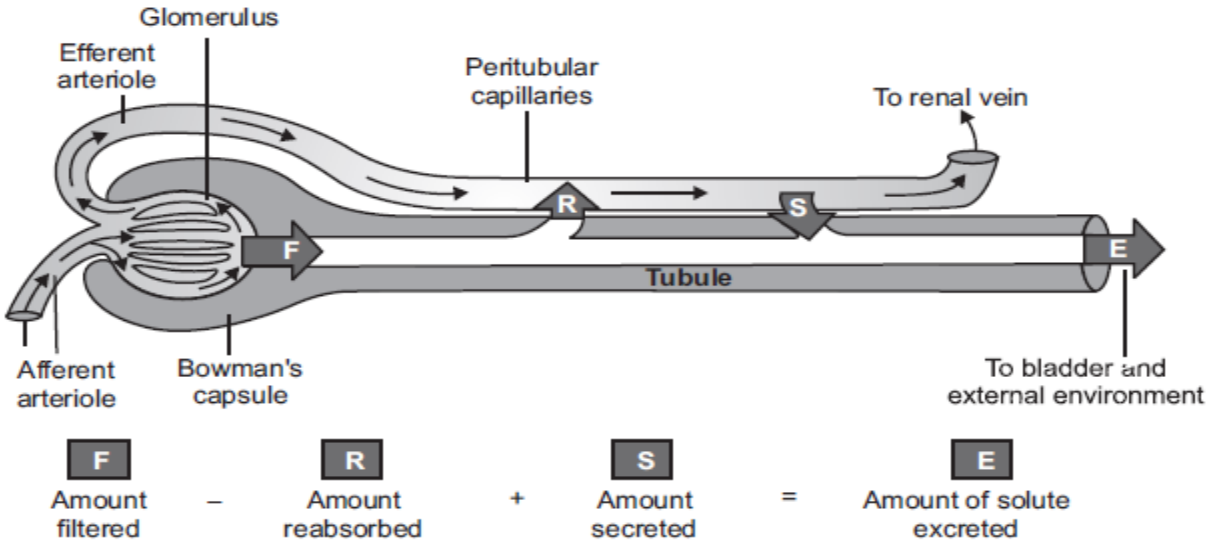
• **Glomerular Filtration:**

- ✓ Receive 25% of cardiac output
- ✓ Filtration rate: 100-120 ml/minute

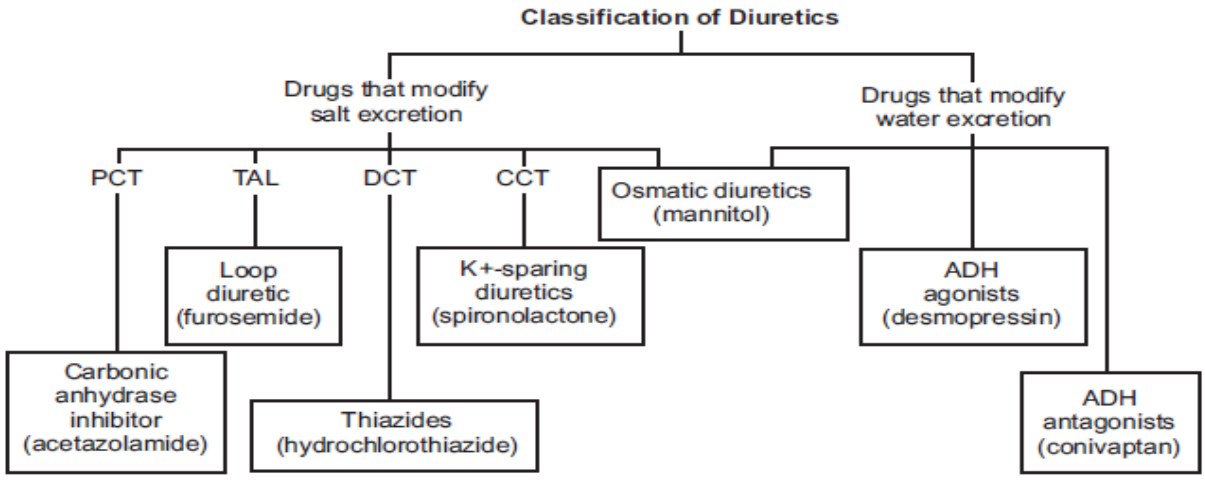
• **Tubular Reaborption:**

- Reabsorption of 99% of glomerular filtrate
- 1.5 L/day of urine.

- **Tubular Secretion:**



CLASSIFICATION OF DIURETICS



Proximal Convoluted Tubule (PCT), Thick Ascending Limb of the loop of Henle (TAL), Distal Convoluted Tubule (DCT) and Cortical Collecting Tubule (CCT).

11.3 SITE AND MECHANISMS OF ACTIONS OF DIURETICS

Diuretics	Site of Action	Mechanism
Osmotic Diuretic	1. Proximal tubules 2. Loop of Henle 3. Collecting duct	Inhibition of water and Na^+ reabsorption.
Carbonic Anhydrase Inhibitor (CA-I)	Proximal tubules	Inhibition of bicarbonate reabsorption.
Loop Diuretic	Loop of Henle (*thick ascending limb*)	Inhibition of Na^+, K^+, Cl cotransport.
Thiazide	Early distal tubule	Inhibition of Na^+, Cl cotransport
K^+ sparing diuretics	Late distal tubule Collecting duct	Inhibition of Na^+ reabsorption and K^+ secretion.

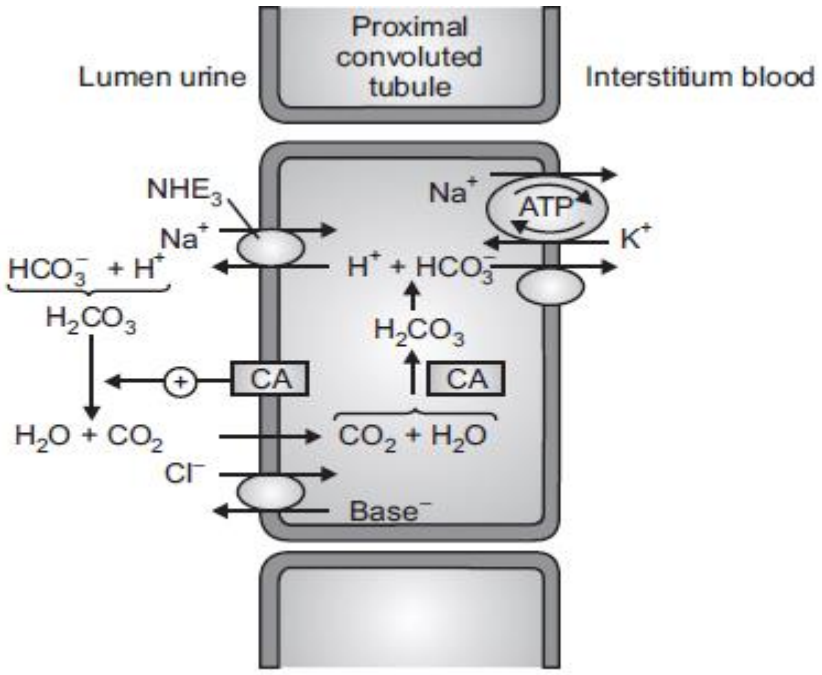
1. Carbonic Anhydrase Inhibitor:

Acetazolamide

Mechanism of Actions:

Kidney: Self Limited Diuresis 2-3 days.

- Carbonic anhydrase catalyzes: $CO_2 + H_2O \rightarrow H2CO3$
- H+ ion produced by the breakdown of H_2CO_3, exchanged for Na^+ and is also
- Combined with HCO_3^- in the lumen of the PCT.
- Inhibition of Bicarbonate (HCO_3^-) reabsorption.
- Reduces Na+ - H+ -exchange NaHCO3 is excreted along with H_2O.



Mechanism of action Carbonic Anhydrase inhibitor

Adverse Effects and Contraindications:

• Metabolic acidosis.

• Renal stones (Phosphate and Calcium stone).

• Renal potassium wasting; (NaHCO3−) enhances K+ secretion.

• Diuresis is self limiting within 2-3 days.

• AE: Drowsiness, paresthesia, disorientation, renal stone (in case of urine alkalinization).

Contraindication:

• Liver cirrhosis (CA-I inhibits conversion of NH3 → to NH4) → NH3 increased encephalopathy.

Indications of CA-I:

• Glaucoma (Eye: not self limiting effect):

o Orally acetazolamide

o Topically dorzolamide, brinzolamide

• Prevent mountain sickness (high altitude) sickness inhibit sec of bicarbonate by the choroid plexus; Acidosis of the CSF results in hyperventilation.

• **Urinary alkalinization:** Preventing uric acid and cystine stones.

• Used for their diuretic effect only if edema is accompanied by significant metabolic alkalosis.

2. Thiazides:

• Hydrochlorothiazide (prototype), Chlorothiazide, Bendroflumethiazide, Chlorthalidone, Metolazone, Indapamide.

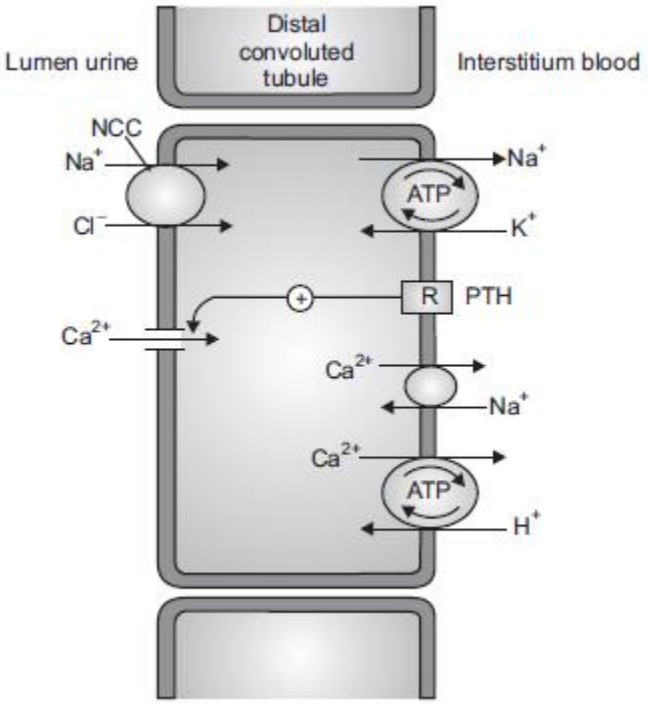
• All are sulfonamide derivatives, t1/2 − 6-12 hrs.

Mechanism of Actions:

• Thiazides are secreted by proximal tubules but works in DCT.

• Inhibit Na+Cl symporter from the lumen to tubular cells ⟶increase Na+, Cl− excretion (and water)

• Some thiazides have weak CA-I effect.



Effects on Electrolytes:

• Increases Na+ and Cl− excretion.

• Hypokalemic metabolic alkalosis; K+ excretion also increase associated with increased Na+ in distal tubules.

• Inhibits uric acid secretion → hyperuricemia and gout.

• Decreases Ca2+ excretion.

• Tends to increase plasma Ca++.

• Retards osteoporotic process.

• Increases Mg2+ excretion.

Adverse Effects:

• Hypo K+ Increased risk of digitalis toxicity.

• Hypo Na+, Hypo Mg++.

• Hyperuricemia caution in gout arthritis.

• Hyperglycemia and hypercholesterolemia→ not favorable for DM and dyslipidemia (although not contraindicated).

• Indapamide has less effect on lipid and uric acid.

• Hypercalcemia (long-term).

• Sexual dysfunction.

Interactions:

• Increases the risk of arrhythmia when combined.

• With digitalis, quinidine and other antiarrhythmias.

• Reduces efficacy of anticoagulant and uricosuric.

• Reduces the efficacy oral antidiabetics.

• NSAID reduces the efficacy of thiazide.

Indications of Thiazides:

• Hypertension (single drug or in combination).

• Chronic, mild-heart failure.

• Edema (loop diuretic is preferable).

• Nephrogenic Diabetes insipidus.

• Prevention of Ca++ excretion in osteoporosis and Calcium nephrolithiasis.

3. Loop Diuretics:

• Furosemide, torasemide, bumetanide: Are sulfonamide derivatives.

• Ethacrynic acid is a phenoxyacetic acid derivative.

• Site of action: thick ascending limb of Henle.

Mechanism:

• Loop diuretics should be excreted into the lumen.

• Inhibits Na+, K+, 2Cl− symporter significantly increases the excretion of Na+, K+, Cl−.

Osmotic gradient for water reabsorption is also decreased → increasing water excretion.

• Ca2+ and Mg2+ are excreted as well.

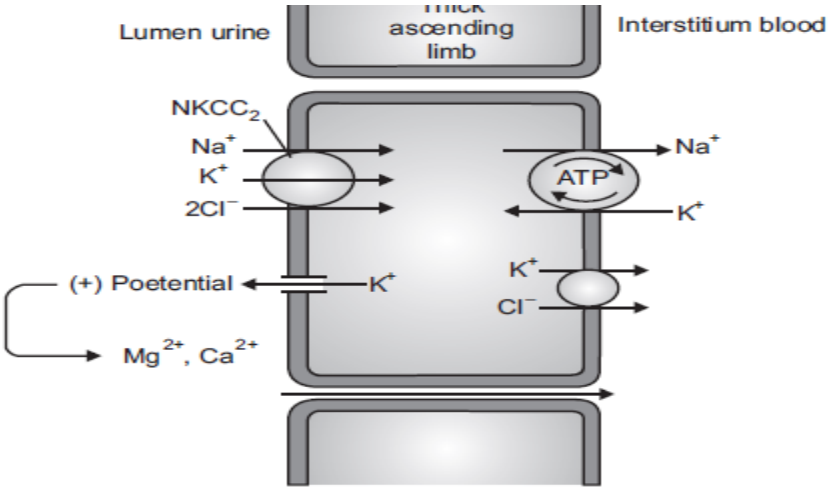


Fig. 11.5: Mechanism of action of Loop diuretics

Adverse effects:

• Hypovolemic metabolic alkalosis.

• Ototoxicity.

• Typical sulfonamide allergy.

Interactions:

• Concomitant use with aminoglycoside or cisplatin increases the risk of nephrotoxicity and ototoxicity.

• PGs are important in maintaining GF; NSAID reduces the effects of diuretics.

• Probenecid reduces the effects of diuretics by inhibiting its secretion into the lumen.

Indications:

• Congestive heart failure (1st line drug).

• Acute pulmonary edema.

• Edema due to renal failure, nephrotic syndrome, ascites.

• Hypercalcemia (that induced by malignancy).

• Severe hypertension.

• Force diuresis during drug/chemical intoxication (drug that excreted through the kidney in active form).

4. Potassium Sparing Diuretics:

(i) Na+ channel inhibitor (Amiloride, triamterene):

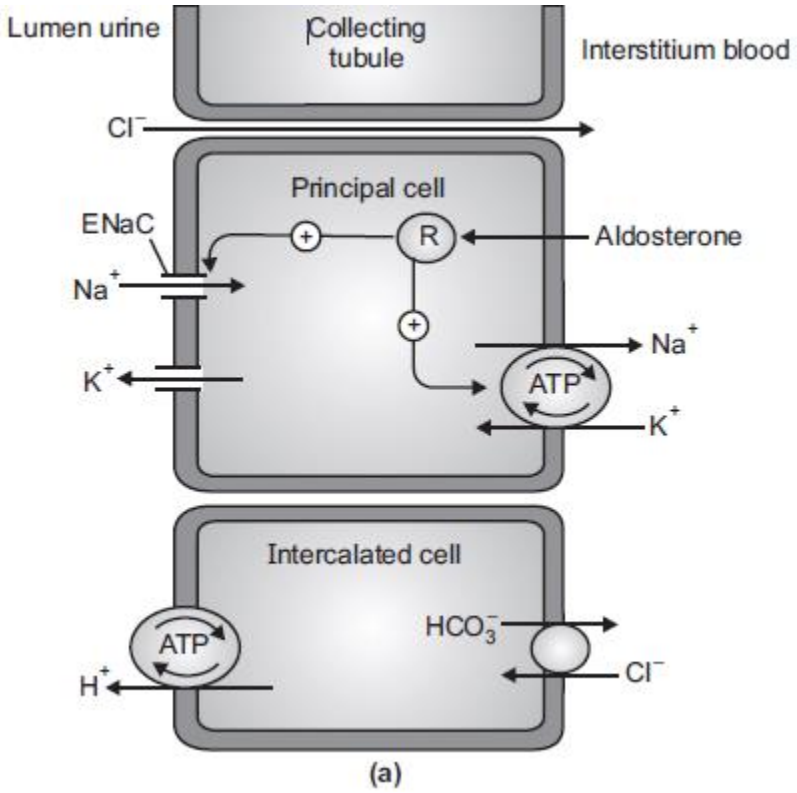
• Inhibit Na+ reabsorption → Na+ excretion.

• Reduced K+ secretion → K+ retention.

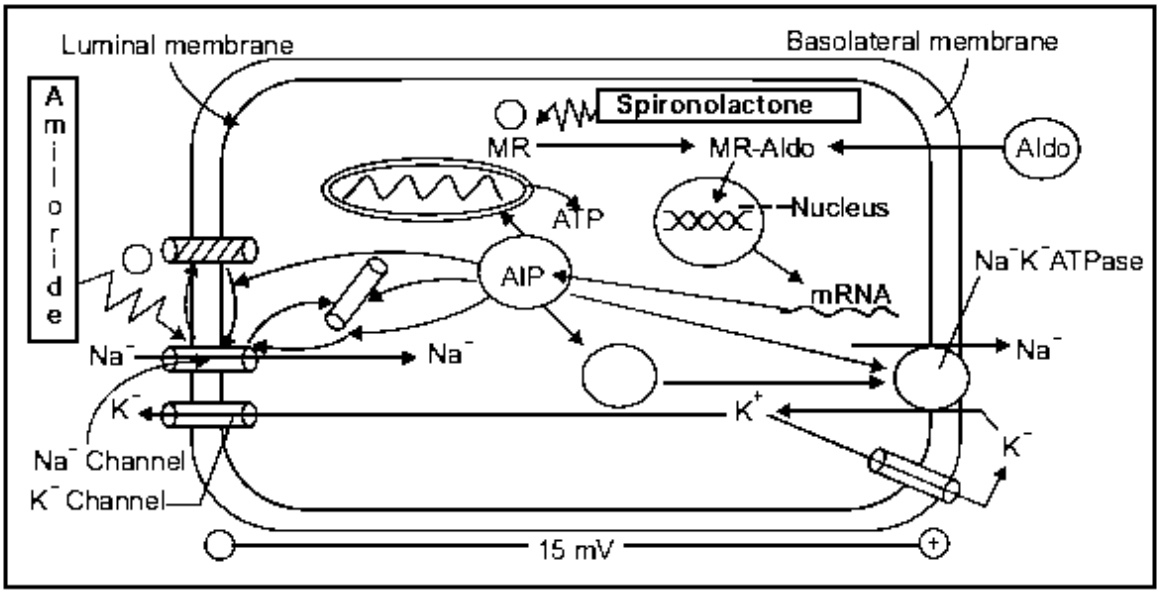
(ii) Aldosterone antagonist (Spironolactone, Eplerenone) Steroid Derivatives:

• Aldosterone induces the expression of Na/K ATPase and Na+ channel.

• Spironolactone and eplerenone blocks aldosterone receptor → reduces Na+ reabsorption and K+ secretion.



(a)



(b)

Fig. 11.6: MoA of Potassium Sparing Diuretics

• Potassium sparing diuretic has a weak diuretic action.

• Usually used in combination with other diuretic:

- ✓ Potentiation of diuretic and antihypertensive effects.
- ✓ Prevents hypokalemia.

• Spironolactone is metabolized to its active metabolite, canrenone.

• Long term use of spironolactone can prevent myocardial hypertrophy and myocardial fibrosis.

Adverse Effects:

• Hyperkalemia

• Antiandrogenic effect

- ✓ gynecomastia,
- ✓ decrease of libido, impotence,
- ✓ Menstrual disturbance.

• Megaloblastic anemia: Triamterene (folate antagonist).

Indications:

• Antihypertension.

• In combination with other antihypertensives.

• To increase the effect and to prevent hypokalemia.

• Aldosteronism (that occur in cirrhosis).

Contraindications/Precautions:

• Conditions that prone to hyperkalemia.

• Renal failure.

• Should never be combined with ACE-inhibition, ARB.

• NSAID, K+ supplementation.

5. Osmotic Diuretics (OD):

• Mannitol (prototype).

• Others rarely used: urea, glycerin, isosorbide.

• Properties of osmotic diuretics:

- ✓ Freely filtrated by glomerulus.
- ✓ Negligible tubular reabsorption.
- ✓ Chemically inert.
- ✓ Usually non-metabolized.

Mechanism of Action:

• OD is filtrated and increases osmotic pressure in tubular lumen.

• Hence, increases excretion of water and electrolytes (Na+, K+, Ca++, Mg++, HCO3-, phosphate) ↑volume of urine and rate of urine flow through the tubule.

• Mannitol can also reduce brain volume and intracranial pressure by osmotically extracting water from the tissue into the blood.

• A similar effect occurs in the eye.

Adverse Effects:

• Removal of water from the I.C compartments → Initial increase of plasma volume → potentially dangerous in heart failure and pulmonary edema → Hypo → Na+ → headache, nausea, vomiting.

• Water excretion → Hypovolemia → Hypernatremia.

• Hypersensitivity reaction.

• Vein thrombosis, pain if extravasation (urea).

• Hyperglycemia, glycosuria (glycerin).

Pharmacokinetics:

• **Mannitol and urea:** Intravenous.

• **Glycerin and isosorbide:** Can be administered orally.

Metabolism:

• Glycerin 80% metabolized.

• Mannitol 20%.

• **Urea, isosorbide:** Not metabolized.

• **Excretion:** Renal.

Indications:

• Glaucoma (rare) ↓ IOP (Intra-Ocular Perssure).

• Brain edema, ↓brain volume and pressure.

• Mannitol and urea are given before and after brain surgery.

• Disequilibrium syndrome after hemodialysis.

• Solute overload in sever hemolysis and rhabdomyolysis.

• Prophylaxis of ATN (acute tubular necrosis) due to contrast media, surgery, and trauma.

• NaCl 0.45% can also be used.

ANTIDIURETICS

An antidiuretic is a substance that helps to control fluid balance in a living body by reducing urination, opposing diuresis.

Antidiuretics: Drug List

• Antidiuretic Hormone (ADH, Vasopressin)

o Desmopressin, Lypressin, Terlipressin

• Thiazide Diuretics:

o Amiloride

• Miscellaneous:

- Indomethacin,
- Chlorpropamide,
- Arbamazepine

Antidiuretic Hormone (ADH)

ADH is a hormone (protein) secreted by posterior pituitary (neurohypophysis). Rate of ADH Release controlled by:

• Osmoreceptors present in hypothalamus.

• Volume receptors present in left atrium, ventricles and pulmonary veins.

• ADH and Desmopressin are ADH Agonists.

• Secretion of ADH increase in response to:

o Plasma osmolarity

o Hypovolemia, hypotension (bleeding, dehydration)

• Demeclocycline and conivaptan are ADH antagonists

• Lithium has ADH antagonist effect but never used for this purpose.

ADH Receptors:

V1 Receptors:

• At all sites except for sites of V2 (i.e. Collecting Duct cells).

• Further classified as V1a and V1b.

V1 (a) Vascular smooth muscles (including that of vasa recta in renal medulla), uterine, visceral smooth muscles, interstitial cells in renal medulla, cortical CD cells, adipose tissue, brain, platelets, liver, etc.

V1 (b) Anterior pituitary, certain areas in brain and in pancreas.

V2 Receptors: More sensitive:

• **Collecting Duct Principal Cells in Kidney:** Regulates their water permeability.

• **Also present in AscLH cells:** Activates Na+K+2Cl cotransporter.

• **Endothelium:** Vasodilator.

ADH: Action on Various Organs

• **Kidneys:**

Acts on CD principal cells---- renders them water permeable --- water absorbed---- concentrated urine (equilibrating with hyperosmolar medulla) passed.

• **Blood Vessels:**

Constricts through V1 receptors: raises blood pressure.

Dilates through V2 receptors: endothelium dependent NO production.

• **GIT:**

Increased peristalsis: evacuation and expulsion of gases.

• **Uterus:**

Contracted by acting on oxytocin receptors.

• **Central Nervous System:**

Endogenous AVP may be involved in regulation of temperature, learning of tasks.

Others:

Induces platelet aggregation, hepatic glycogenolysis. Release of factor VIII and von Willebrand's factor from vascular endothelium: V2 mediated.

Mechanism of Action:

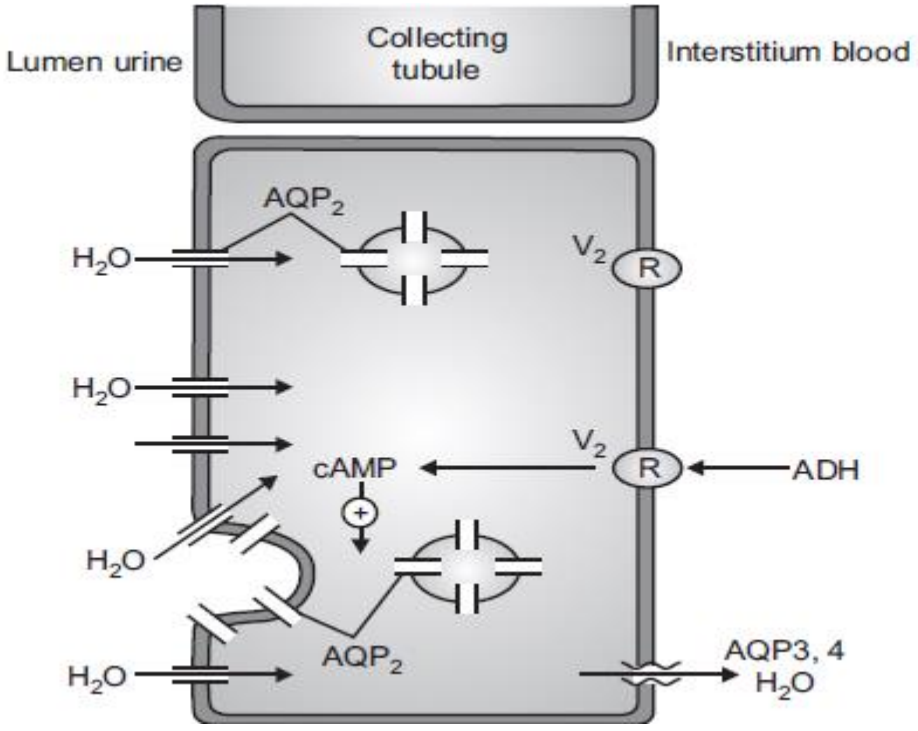
• Works in ascending limb of Henle's loop and collecting ducts.

• Two kind of receptors:

- ✓ V1: Vascular smooth muscle − vasoconstriction.
- ✓ V2: Kidney − increase water permeability of tubular epithelium – water reabsorption.

• ADH facilitates water reabsorption from the collecting tubule by: activation of V2 receptors (coupled to GS, stimulate AC) increase cAMP.

• Cause insertion of additional aquaporin AQP2 water channels into the luminal membrane in this part of the tubule.



Clinical uses of ADH Agonists:

• ADH and desmopressin reduce urine volume and concentrate it, are useful in Pitutary Diabetes Insipidus (DI).

• Gastrointestinal bleeding due to portal hypertension.

ADH Antagonists:

• Conivaptan is an ADH inhibitor at V1a and V2 receptors.

• Demeclocycline and Li inhibit the action of ADH at some point distal to the generation of cAMP and presumably the insertion of water channels into the membrane.

Clinical uses of ADH Antagonists:

• Oppose the actions of ADH and other naturally occurring peptides (certain tumors; small cell carcinoma of the lung) that act on the same V2 receptors, leads to significant water retention and dangerous hyponatremia.

• Syndrome of inappropriate ADH secretion.

• (SIADH) can be treated with demeclocycline and conivaptan.

AVP (Arginine vasopressin) Interactions:

• **Lithium, demelocycline:** Partially antagonise AVP action (limiting cAMP formation).

• Used in patients with inappropriate ADH secretion.

• **NSAIDs (Indomethacin):** Augments AVP (increased renal PG synthesis).

• Carbamazepine, chlorpropamide: potentiates AVP action on kidney.

AVP: Uses

Based on V2 Actions:

• Diabetes Insipidus (Neurogenic).

• Bedwetting in children and nocturia in adults.

• Renal Concentration Test.

• Hemophilia, von Willebrand's Disease.

Based on V1 Actions:

• Bleeding Esophageal Varices.

• Before abdominal radiography.

Vasopressin: Adverse Effects

• Selective drugs produce lesser side effects.

• Transient headache and flushing: frequent.

• **Local Application:** Nasal irritation, congestion, rhinitis, ulceration, epistaxis.

• **Systemic Side effects:** belching, nausea, vomiting, abdominal cramps, pallor, urge to defecate, backache. In females (uterine contraction) Fluid retention, hyponatremia.

Thiazide: Hydrochlorthiazide

• Paradoxical Effect.

• **Furosemide:** effective but less desirable: short and brisk action.

• Effective in both neurogenic as well as nephrogenic DI.

Mechanism of Action:

1. Similar to Salt Restriction:

• State of sustained electrolyte depletion.

• Glomerular filtrate completely reabsorbed iso-osmotically in PT.

• Urine passing has low solutes − presented to cortical DT − salt reabsorption decreases − less dilute urine presented to CD − same is passed out.

2. Reduces glomerular filtration rate − reduced fluid load on tubules.

Other Antidiuretics:

Indomethacin:

• Decreases renal prostaglandin synthesis, reduced polyuria in nephrogenic DI.

• Combined with thiazide +/- amiloride.

Chlorpropamide:

• Long acting sulfonylurea oral hypoglycaemics.

• Effective in neurogenic DI: sensitizes kidney to ADH.

Carbamazepine:

• Anticonvulsant.

IMPORTANT QUESTIONS

Very Short Answer Type Questions

1. What are haematinics?
2. Define anemia
3. What are the toxics effects of iron?.
4. What are plasma expenders?
5. What are coagulants?
6. What is the use of protamine sulphate?
7. What are anti-coagulants?
8. Define shock.
9. What are anti-platelets?
10. Write sources of folic acid.

Short Answer Type Questions

1. Describe the role of iron in blood formation.

2. Explain the pharmacology of cynocobalamine (vitamine B_{12}).

3. Discuss the erythropoisis, write the pharmacology of erythropoietin.

4. Describe the vitamin K in coagulation. Write the pharmacology of fibrinogen.

5. Explain anti-coagulants, classify them, and write the pharmacology of heparin.

6. Describe the fibrinolytics, classify and pharmacology of streptokinase.

7. Write a note on plasma expenders.

Long Answer types Questions

1. Write a note on plasma volume expanders.
2. Classify diuretics. Discuss the mechanism of actions and uses of thiazide diuretics.
3. Discuss the pharmacology of frusemide.
4. Write down the mode of action, adverse effect and therapeutic uses of loop diuretics.
5. Write a note on osmotic diuretics.
6. Classify diuretics with examples. Explain the mechanism of action, adverse effects and uses of Acetazolamide.
7. MOA, ADR and uses of vasopressin.