CHAPTER 10

CARDIOVASCULAR SYSTEM

INTRODUCTION

The cardiovascular system consists of the heart, blood vessels including renal mechanism which plays a crutial role in maintaining blood pressure. Heart pumps approximately 5 liters of blood each minute. Heart is responsible for transporting oxygen, nutrients, hormones through out the body and also cellular waste products towards excretory organ (Kidneys etc). Cardiovascular disease includes a number of conditions affecting the structures or function of the heart. They can include Coronary artery disease (narrowing of the arteries), Heart attack, Abnormal heart rhythms or arrhythmias, Hyper or hypotension, Heart failure, Angina pectoris etc. Abnormality in blood and lipid level also affects the functions of the heart.

CHAPTER 10.1

HAEMATINICS / ANTIANEMICS

Haematinics or antianemics are agents which are required for the formation of blood especially in case of anaemia.

ANAEMIA

Anaemia is due to deficient numbers of circulating RBCs or reduction in haemoglobin content per unit of body volume.

Causes of Anaemia:

- Blood loss
- Nutritional deficiency
- Complex hereditary deficiency
- Reduction in RBC production

Haematinics are

- **Iron**
- **Folic acid**
- **Vitamin B_{12}**

IRON

Source: Meat, liver, egg yolk, dry beans, jaggery and banana

Daily iron requirement: 1-2.5mg

ABSORPTION, TRANSPORT, STORAGE & ELLIMINATION Fig.10.1.1

- Iron is normally absorbed in the duodenum and proximal jejunum
- Non-heme iron in foods and iron in inorganic iron salts and complexes gets reduced to ferrous (Fe2+) iron before absorption by the intestinal mucosal cells.
- Iron crosses the intestinal mucosal cell by active transport
- Absorbed iron is transported from the mucosal cell to the plasma via a carrier called **transferrin** or can be stored in the mucosal cell as **ferritin** along with specialized storage protein called **apoferritin.**

Note: If iron is not needed for the body for that movement, then it will be stored in the mucosal cell as **ferritin** along with specialized storage protein called **apoferritin.**

If iron is needed by the body then the absorbed iron is directly transferred to plasma and carried to bone marrow for production of **hemoglobin.**

TRANSPORT:

Iron is transported in the plasma bound to a carrier protein called **transferrin**

The **transferrin-ferric iron** complex enters maturing erythroid cells via receptor mechanism.

Transferrin-iron complex undergo internalization, thus iron gets released in to the cell.

STORAGE:

Iron binds avidly to a protein, **apoferritin,** and forms the complex **ferritin**. It is stored in intestinal mucosal cells and in macrophages in the liver, spleen, and bone.

ELLIMINATION:

Small amounts of iron are lost by exfoliation or shedding of intestinal mucosal cells into the stool, and small traces are excreted in bile, urine, and sweat. Maximum loss is 1 mg per day.

Fig.10.1.1

Total body iron: Males: 4.5 g & Female: 2.5g

IRON DEFICIENCY ANAEMIA

Iron forms an important nucleus for the formation of iron-porphyrin heme ring, which along with globin forms hemoglobin.

Hemoglobin reversibly binds oxygen and carries this oxygen from the lungs to other tissues. If there is absence of adequate iron, small erythrocytes will be formed with insufficient hemoglobin, which gives rise to microcytic hypochromic anemia.

Symptoms of iron deficiency anemia is pallor, fatigue, dizziness, exertional and dyspnea

TREATMENT: Iron therapy

IRON THERAPY

Iron therapy can be done either by administering orally or parenterally (i.v / deep i.m)

- Oral iron therapy
- Parenteral iron therapy

ORAL IRON THERAPY

INDICATIONS FOR ORAL IRON THERAPY

- Mild to moderate iron deficiency anaemia
- For those who can tolerate oral iron therapy
- Iron deficiency anaemia due to hookworm infestation
- In pregnancy and lactation
- In infants, especially premature infants; children during rapid growth periods

ORAL IRON PREPARATIONS (Table.10.1.1)

Table.10.1.1

Oral Iron Preparation	Dosage forms	Elemental Iron per Tablet	Adult Dosage (Number of Tablets per Day)
Ferrous sulfate hydrated & Dessicated	**325 mg & 200mg**	**65mg for both**	**3-4**
Ferrous succinate	**100mg**	**35 mg**	**3-4**
Ferrous gluconate	**325 mg**	**36mg**	**3-4**
Ferrous fumarate	**200 mg & 325 mg**	**66mg & 106mg respectively**	**2-3**

USES

Iron deficiency anaemia

ADVERSE EFFECTS

- Metallic taste
- Nausea and anorexia
- Staining of teeth (with liquid preparation)
- Gastric irritation, epigastric discomfort and abdominal cramps
- Constipation (due to its astringet property) or diarrhea (due to its irritant property)

DRUG INTERACTION

- Iron absorption is decreased by the presence of chelators, calcium, antacids or complexing agents in the intestinal lumen.
- Iron absorption is increased in the presence of vitamin C (Ascorbic acid).

CONTRAINDICATIONS

History of hypersensitivity to the drug

Nursing implication

- A patient taking oral iron preparations passes black colored stools and it is normal, hence advice the patient not too get scared and get confuse with passing of blood in stool.
- Advice the patient to avoid calcium preparation and antacid intake when consuming iron preparation.

PARENTERAL IRON PREPARATIONS

INDICATIONS FOR PARENTERAL IRON THERAPY

- For those who are unable to tolerate or absorb oral iron
- Patients with severe and chronic blood loss who cannot be maintained with oral iron alone.
- In those patients gastrectomy conditions and previous small bowel resection, inflammatory bowel disease involving the proximal small bowel, and other malabsorption syndromes.

Do you know how to calculate iron requirement for the body?

4.4 × Body weight (kg) × HB Deficiency (gm/dl)

PARENTERAL IRON PREPARATIONS

- Iron dextran
- Iron sorbitol

Table.10.1.2

IRON DEXTRAN (50 mg of elemental iron per milliliter of solution)	**IRON SORBITOL** (75 mg of elemental iron per milliliter of solution)
1. High molecular weight	1. Low molecular weight
2. Deep i.m/i.v	2. Only deep i.m (Strictly not to be given i.v)
3. Lymphatic absorption	3. No Lymphatic absorption
4. Locally get bound to tissue	4. Not Locally get bound to tissue
5. Not bind to transferin	5. Bind to transferin
6. Not gets excreted	6. Excreted in urine
7. Taken up by macrophages	7. Not Taken up by macrophages

USES

- Iron deficiency anaemia
- In megaloblastic anaemia (along with vit B_{12} of folic acid)

PARENTERAL IRON PREPARATIONS AND ROUTE OF ADMINISTRATION

- Iron dextran: 50 mg elemental iron/mL
- Iron sorbitol: 75mg elemental iron/mL

Other parenteral iron preparation

- Iron sucrose: 20 mg elemental iron/mL

- Parenteral (Sodium ferric gluconate complex) : 12.5 mg elemental iron/mL

ADVERSE EFFECTS

- Pain at IM site
- Staining of skin (brown discoloration of the tissues overlying the injection site)
- Fever , headache and joint pains
- Flushing and palpitation
- Chest pain
- Dyspnoea
- Anaphylactoid reactions

CONTRAINDICATIONS

Patients with a strong history of allergy and patients who have previously received parenteral iron are more likely to have hypersensitivity reactions following treatment with parenteral iron dextran.

Nursing implication

- Owing to the risk of a hypersensitivity reaction, a small test dose of iron dextran should always be given before full intramuscular or intravenous doses are given.
- To prevent staining of skin use **"Z"** track technique while giving iron dextran deep i.m.
- When using the Z-track method, you displace the tissue before you insert the needle. Once the needle's withdrawn, the tissue's restored to its normal position. this traps the drug inside the muscle and prevents any leakage. The benefit: The patient gets the full dose of medication.

Follow these steps when administering a drug I.M. using the

Z-track method:

- Verify the drug order on the patient's chart.
- Wash your hands.
- Reconstitute the drug as needed. Check the drug's color, clarity, and expiration date.
- Draw the correct amount of drug into the syringe using aseptic technique.
- After drawing up the dose, replace the original needle with a sterile needle of the appropriate length for the patient's size.

- Put on gloves.
- Confirm the patient's identity using two identifiers.
- Select an injection site: the ventrogluteal or deltoid site in adults, the vastus lateralis site in infants and toddlers, and the vastus lateralis or deltoid site in children.
- Position the patient so that the muscle at the injection site relaxes.
- Clean the site with an alcohol pad and let it thoroughly dry.
- Use your nondominant hand to pull the skin downward or laterally to displace the tissue about 1 inch **Fig.10.1.2a**
- With the needle at a 90-degree angle to the site, pierce the skin using a smooth, steady motion **Fig.10.1.2b**
- Aspirate for 5 to 10 seconds to ensure that you haven't hit a blood vessel.
- Inject the drug slowly at a rate of 10 seconds/mL of medication.
- Once the drug is completely instilled, wait 10 seconds before withdrawing the needle.
- Withdraw the needle with a smooth, steady motion and release the skin to its original position. (In the illustration, the dotted line represents the needle track.) Use dry gauze to apply very gentle pressure to the puncture site **Fig. 10.1.2c**

Fig.10.1.2a, 10.1.2b & 10.1.2c

- Never massage a Z-track injection site. This may cause irritation or force the drug into subcutaneous tissue.
- Assess the site immediately after administering the injection and again 2 to 4 hours later.
- Properly dispose of all used equipment and supplies.

ACUTE IRON TOXICITY AND TREATMENT

It is seen in children who accidently consumes more than 10 tablets or while parenteral iron therapy, if by i.v is > 60mg/kg iron, then acute iron toxicity manifests.

Signs and symptoms includes

Necrotizing gastroenteritis, with vomiting, abdominal pain, and bloody diarrhea followed by shock, lethargy, and dyspnea.

Usually patient recovers for a short period followed by severe metabolic acidosis, coma, and death.

TREATMENT

- Induce vomiting and perform gastric lavage
- Egg yolk & milk can be given if excess of iron has been consumed orally.

- Specific antidote for iron poisoning is **Desferrioxamine** (iron chelating agent) to remove absorbed iron or already infused excess of iron.

  Desferrioxamine dose: 0.5 -1gm (50mg/kg) i.m repeated 4-12 hourly and in case of shock, 10-15mg/kg/hour can be infused.

CHRONIC IRON TOXICITY AND TREATMENT

Chronic iron toxicity is due to iron overload and is also known as hemochromatosis, results when excess of iron is deposited in the heart, liver, pancreas, and other organs which can lead to organ failure and death.

It most commonly occurs in patients with inherited hemochromatosis, a disorder characterized by excessive iron absorption, and also in patients who receive many blood transfusions over a long period of time.

Treatment

- Intermittent phlebotomy (blood letting). About one unit of blood can be removed every week or so until all of the excess iron is removed.
- Parenteral deferoxamine can be useful only if it cannot be managed by phlebotomy.

VITAMIN B_{12}

Vit B_{12} is needed for maturation of RBC and deficiency of Vit B_{12} leads to megaloblastic anaemia, gastrointestinal symptoms, and neurologic abnormalities

- Daily requirement→ 1-3 µg
- Source : microbially derived vitamin B12 in meat (especially liver), eggs, and dairy products.
- Function : Purine & pyramidine synthesis & Cell growth & multiplication
- Absorption → forming a complex with intrinsic factor of castle, a glycoprotein secreted by the parietal cells of the gastric mucosa.
- Storage: Liver
- Transportion→ By binding to transcobalamin II in plasma
- Excretion→ bile and only trace amounts of vitamin B12 are normally lost in urine and stool.

Vit B_{12} Deficiency

Megaloblastic anemia (macrocytic anemia) with mild or moderate leukopenia or thrombocytopenia (or both).

Vit B_{12} Deficiency also leads to neurologic syndrome that usually begins with paresthesias and weakness in peripheral nerves and progresses to spasticity, ataxia, and other central nervous system dysfunctions.

VIT B_{12} PREPARATIONS AND ROUTE OF ADMINISTRATION

- Oral cyanocobalamin: 100, 500, 1000 g tablets, 100, 250, 500 g lozenges
- Nasal cyanocobalamin: 5000 g/mL (500 g/spray)
- Parenteral (cyanocobalamin): 100, 1000 g/mL for i.m or s.c injection
- Parenteral (hydroxocobalamin): 1000 g/mL for i.m injection only

Therapeutic uses

- Vit B12 deficiency anaemia
- Pernicious anaemia (failure of secretion of intrinsic factor)

Adverse effects

- Allergic reactions

FOLIC ACID

It should be noted that the reduced forms of folic acid is required for essential biochemical reactions that provide precursors for the synthesis of amino acids, purines, and DNA.

- **Source :** Liver, kidney, leafy vegetables,yeast and egg
- **Daily reqirement:** 0.1 mg
- **Absorption:** Small intestine
- **Storage:** 5–20 mg of folates is stored in the liver and other tissues.
- **Exretion:** Stool and urine

USES:

- Megaloblastic anaemia
- To Prevent neural tube defects

FOLIC ACID PREPARATIONS AND ROUTE OF ADMINISTRATION

Oral: 0.4, 0.8, 1 mg tablets

Parenteral: 5 mg/mL for injection

CHAPTER 10.2

DRUGS USED IN DISORDERS OF COAGULATION

Drugs that are used in disorders of coagulation or clotting mechanism can be studied under following headings

- **Anti-coagulants and Anti-platelets**
- **Fibrinolytics / Thrombolytics**
- **Anti-fibrinolytics and other Coagulants or Procoagulants**
- **Styptics**

ANTI-COAGULANTS AND ANTI-PLATELETS

Drugs affecting clotting factors inhibiting the blood coagulation are called as anti-coagulants. Drugs affecting platelet function to inhibit blood clotting are called as anti-platelets

ANTI-COAGULANTS

Anticoagulants can be classified as oral anti-coagulant and parenteral anti-coagulant.

- **Oral anti-coagulant:** Warfarin
- **Parenteral anti-coagulant:**

1. **Indirect thrombin inhibitors:** Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) and fondaparinux
2. **Direct thrombin inhibitors:** Lepirudin, Bivalirudin, Argatroban and Melagatran

ORAL ANTI-COAGULANT
WARFARIN

- **Warfarin** is a synthetic derivative of dicoumarol, a 4-hydroxycoumarin-derived mycotoxin anticoagulant originally discovered in spoiled sweet clover-based animal feeds. Isolated from clover leaves
- It is structurally related to vitamin K

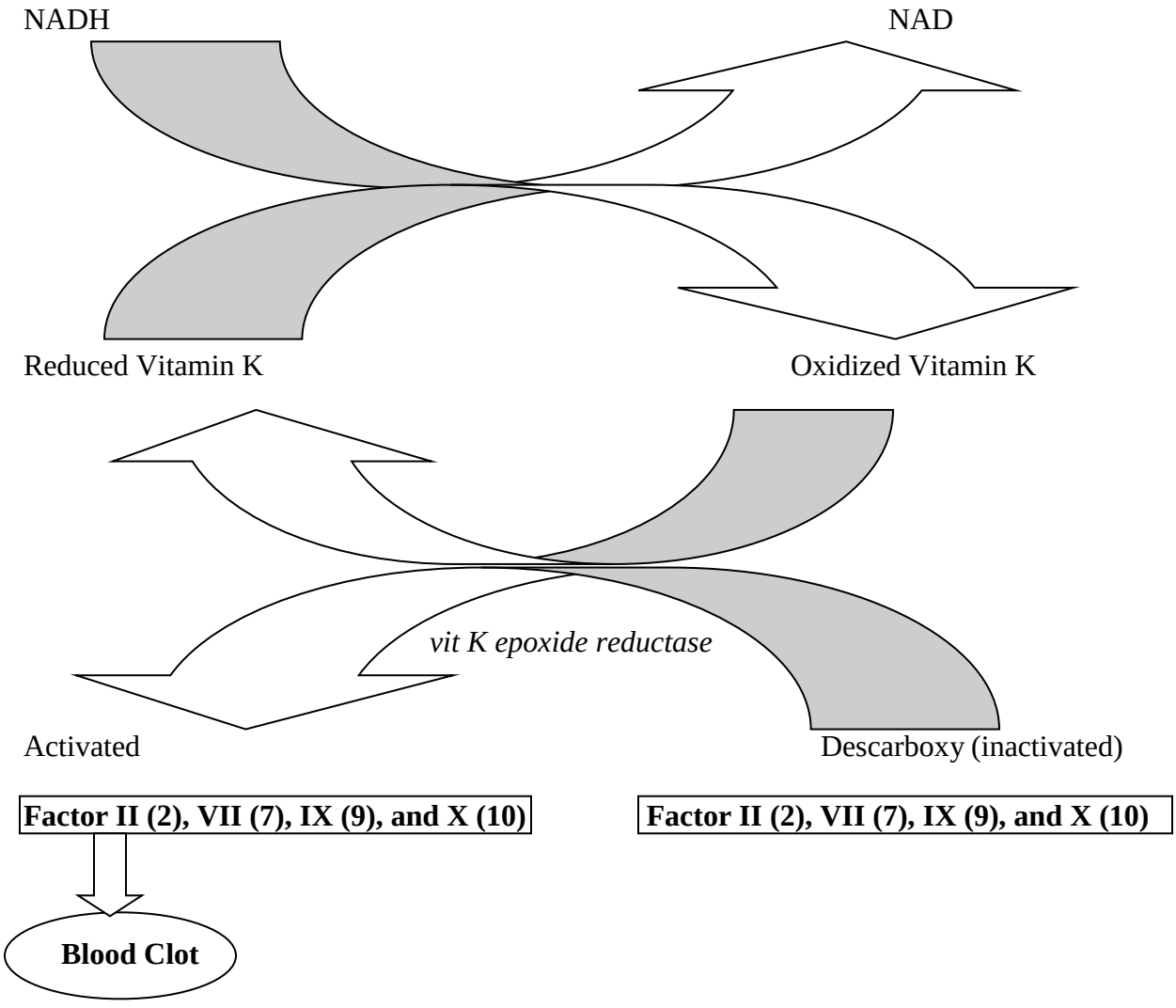
MECHANISM OF ACTION

- Coagulation factors (vit K dependent clotting factors) II (2), VII (7), IX (9), and X (10) are synthesized mainly in the liver.

- They are inactive unless they are get carbon dioxide (CO_2), oxygen (O_2) and reduced vitamin K.

- The oxidized vitamin K gets reduced by an enzyme called *vit K epoxide reductase* (VKOR) to form reduced vit K which helps in carboxylation of factors II (2), VII (7), IX (9), and X (10) resulting in blood clot. **(Fig 10.2.1)**

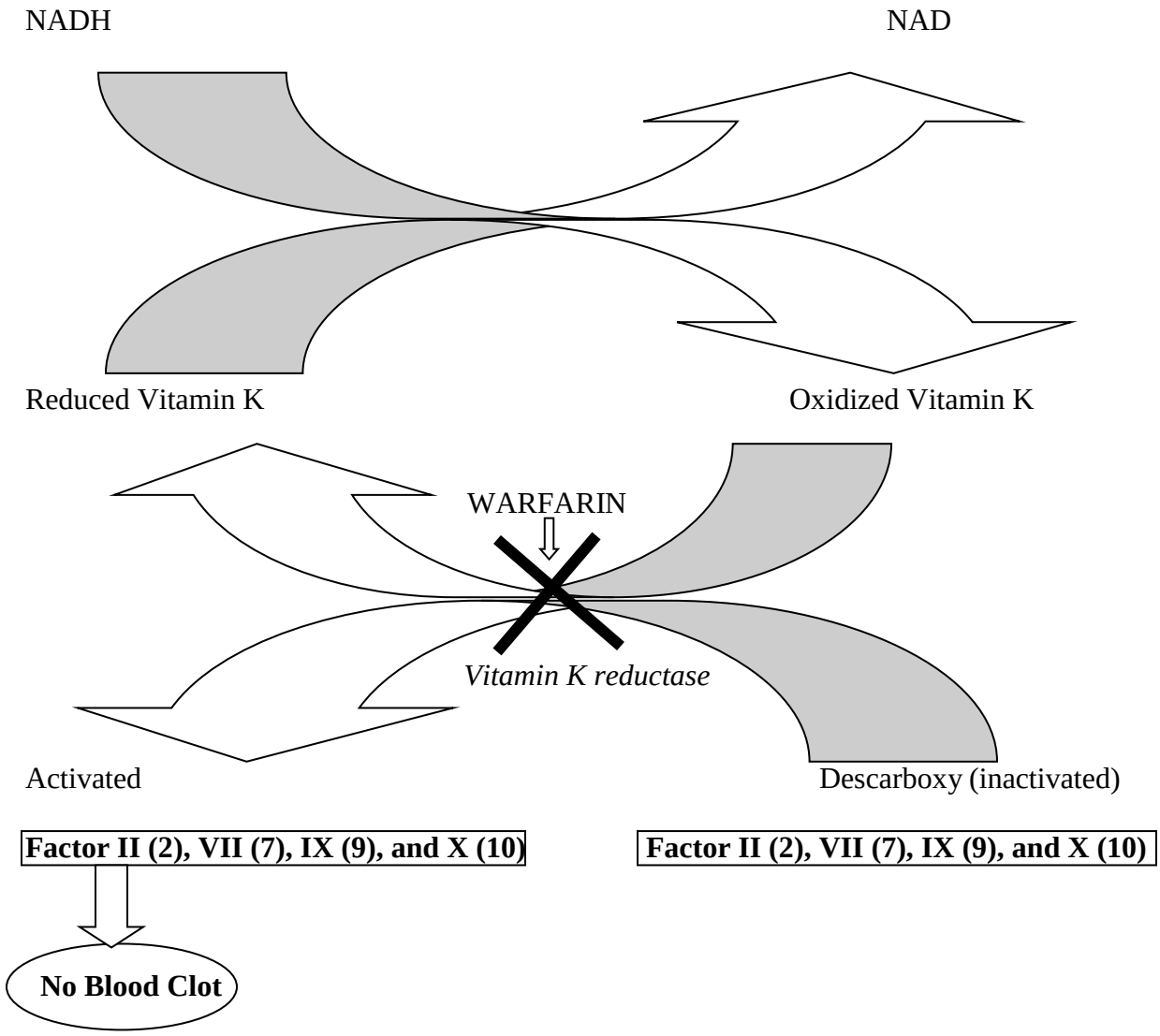
MECHANISM OF BLOOD CLOT IN PRESENCE ON VIT K



(Fig 10.2.1)

- Warfarin inhibits *vit K epoxide reductase* and prevents the conversion of oxidized vitamin K to reduced vit K, hence there will be no activation of clotting factors vit K dependent clotting factors II (2), VII (7), IX (9), and X (10) and hence prevents blood coagulation. **(Fig 10.2.2)**

MECHANISM OF ACTION OF WARFARIN



(Fig 10.2.2)

USES

- Acute deep vein thrombosis or pulmonary embolism

- Venous thromboembolism

- Patients with acute myocardial infarction, prosthetic heart valves (defect in tricuspid, mitral valves pulmonary or aortic valves) and chronic atrial fibrillation.

DOSE AND ROUTE OF ADMINISTRATION

- The usual adult dose of warfarin is 5 mg/day for 2–4 days, followed by 2–10 mg/day as indicated by measurements of the International Normalized Ratio (INR).

Note: Warfarin usually is administered orally but also can be given intravenously without dose modification.

- Warfarin dose adjustment is necessary to get good therapeutic response as shown in **Table 10.2.1**

INTERNATIONAL NORMALIZED RATIO (INR) FOR DOSE REGULATION

Table 10.2.1

INDICATION	INR
Deep Vein Thrombosis	2.0-3.0
Atrial Fibrillation	2.0-3.0
Myocardial Infarction	2.0-3.0
Mechanical Heart Valves	2.5-3.5

DRUG INTERACTION

- Amiodarone, azole antifungals, cimetidine inhibits the other liver cytochrome metabolizing enzymes and may result in high plasma levels of warfarin leading to warfarin toxicity.

- Aspirin and warfarin competes for the same binding site of plasma proteins in which aspirin succeeds and the unbound free warfarin plasma concentration leads to warfarin toxicity.

- Oral contraceptives and barbiturates increase warfarin metabolism and reduce warfarin effect

CONTRAINDICATION

Pregnancy as warfarin crosses placental barrier and cause birth defects.

WARFARIN TOXICITY AND ITS TREATMENT

Bleeding is the major toxicity of warfarin leading to intracranial hemorrhage, epistaxis (bleeding from nose), hematuria (passing of blood in urine), GI bleeding etc.

TREATMENT

- First withhold the drug and the therapy is done as shown in the **Table 10.2.1**

Table 10.2.2

Criteria	Treatment
• If the INR is above the therapeutic range but <5 and the patient is not bleeding or in need of a surgical procedure	• Discontinued warfarin temporarily and it can be restarted at a lower dose once the INR is within the therapeutic range.
• If the INR is ≥5	• Specific antidote - vitamin K1 (*phytonadione*) can be given orally at a dose of 1–2.5 mg (for an INR of 5–9) or 3–5 mg (for an INR >9).
• If the INR is ≥20	• Transfusion of fresh frozen plasma (10–20 mL/kg), supplemented with 10 mg of vitamin K1, given by slow intravenous infusion.

Nursing implication

- Intramuscular injection is not recommended because of the risk of hematoma formation.
- Prior to initiation of therapy, check laboratory tests along with obtaining patient's history and physical examination to access congenital coagulation factor deficiency, thrombocytopenia, hepatic or renal insufficiency, vascular abnormalities, etc.
- INR has to be calculated from the patient's Prothrombin Time (PT) to monitor efficacy and compliance.
- Watch for signs of bleeding and if any withhold the drug and inform the doctor immediately.

PARENTERAL ANTI-COAGULANT
UNFRACTIONATED HEPARIN (UFH)

- Heparin is a sulphated carbohydrate
- It is strongest organic acid present in body.
- It has High Molecular Weight → MW 10,000-20,000. It is also called as Unfractionated heparin (UFH)

- It is found in secretory granules of mast cells
- Commercial heparin is extracted from porcine intestinal mucosa and bovine lung.
- Commercially available heparin is purified from bovine lungs
- It acts both in vitro and in vivo

MECHANISM OF ACTION (Fig 10.2.3)

Anticoagulant actions:

- Antithrombin is synthesized in the liver and circulates in plasma.
- Antithrombin inhibits several coagulation *proteases* of the intrinsic and common pathways including factor thrombin (IIa (2a)), IXa (9a) and (IXa) 10a, but very less activity on factor VIIa (7a).
- More precisely, this reaction can be called as **thrombin-antithrombin reaction**
- Heparin (especially high molecular weight) serves as template for thrombin-antithrombin and brings conformational changes in antithrombin so that the antithrombin can able to inhibit coagulation *proteases* (IIa (2a)), IXa (9a) and (IXa) 10a and VIIa (7a).
- Low molecular weight heparin brings conformational changes in antithrombin so as to inhibit factor (IXa) 10a operating of intrinsic pathway, but does not inhibit thrombin (IIa) of extrinsic pathway.

(Fig 10.2.3)

Difference between High Molecular Weight (HMW) and Low Molecular Weight heparin (LMW) (Table 10.2.3)

(Table 10.2.3)

High Molecular Weight heparin	**Low Molecular Weight heparin** **(E.g.** Dalteparin, Ardeparin, Reviparin, Nadroparin, Enoxaparin, and Tinzaparin,) **MESSAGE TO STUDENTS :** Formula to remember **Low Molecular Weight heparin** is **"DARNET",** the names of all the drug ends with **"parin",** you have to remember **Dalte, Arde, Revi, Nadro, Enoxa,** and **Tinza.**

1. Molecular weight: 10,000-20,000	1. Molecular weight: 3,000-4,000
2. Inhibit both factor Xa and IIa	2. Selectively inhibit factor Xa but not factor IIa
3. Prolongs activated partial thromboplastin time (aPTT) / clotting time	3. Does not prolongs activated partial thromboplastin time (aPTT) / clotting time
4. High incidence of thrombocytopaenia	4. Low incidence of thrombocytopaenia
5. Less subcutaneous bioavailability	5. Better subcutaneous bioavailability
6. Shorter plasma $t_{1/2}$	6. Longer and more exponential plasma $t_{1/2}$

2) Anti-platelet actions:

- High molecular weight heparin and high dose of heparin inhibits platelet aggregation and cause thrombocytopaenis and hence prolongs activated partial thromboplastin time (aPTT) / clotting time

3) Clears lipaemia:

- Heparin promotes release of *lipoprotein lipase* → hydrolyses triglycerides and VLDL in plasma which then pass to tissue→ hence plasma lipid gets cleared.

SYNTHETIC HEPARIN DERIVATIVES

Fondaparinux

It is a synthetic pentasaccharide

It causes inhibition of factor Xa by antithrombin but does not cause inhibition of thrombin due to its short length.

USES

- Venous thrombosis or thromboembolism
- Pulmonary embolism
- Unstable angina or acute
- Myocardial infarction
- During and after coronary angioplasty or stent placement, and during surgery requiring cardiopulmonary bypass.
- **Fondaparinux** subcutaneously is administered for thromboprophylaxis of patients undergoing hip or knee surgery and for the therapy of pulmonary embolism and deep venous thrombosis.

DOSE AND ROUTE OF ADMINISTRATION

- Administration - parenteral- only i.v or deep s.c. (Strictly do not inject i.m)
- 5000 units bolus injection followed by 1200–1600 units/h by an infusion pump for venous thromboembolism
- A total daily dose of ~35,000 units subcutaneous administration as divided doses every 8–12 hours for long-term management of patients in whom warfarin is contraindicated.

ADVERSE EFFECTS

- Bleeding
- Heparin-Induced Thrombocytopenia
- Reversible alopecia may occur
- Liver transaminase level may rise
- Long term use cause may cause osteoporosis
- Rarely it may cause hypersensitivity reaction may occur

HEPARIN TOXICITY AND ITS TREATMENT

In case of threatening hemorrhage due to heparin overdose or toxicity, slow intravenous infusion of protamine sulfate (a mixture of basic polypeptides) that bind tightly to heparin and thereby neutralize its anticoagulant effect. Protamine is obtained from sperm of some fish and is pecific antidote for heparin toxicity.

Dose: ~1 mg of protamine (1% solution) for every 100 units of heparin remaining in the patient, giving it intravenously at a slow rate (25 mg up to 50 mg over 10 -15 minutes). Repeat APTT in 20 min. and 1 hr.

Nursing implication

Protamine sulfate can cause severe, anaphylactoid reactions. Use this agent only when severe bleeding warrants it. Have resuscitation equipment nearby.

In patients receiving subcutaneous heparin, it may be necessary to repeat the protamine sulfate infusion after 1 hr. because of variable heparin absorption.

DRUG INTERACTION

- Heparin + Warfarin: Increased bleeding tendency.
- Heparin if used concurrently with either streptokinase or Tissue plasminogen activator (t-PA) results in serious hemorrhage.

CONTRAINDICATION

- History of drug allergy
- Bleeding disorder
- Severe hypertension, threatened abortion, Piles, G.I bleeding, SABE
- During ocular and neurosurgery
- Chronic alcohol and liver failure

Note: Heparin does not cross the placenta and hence is not associated with fetal malformations; therefore it is the drug of choice for anticoagulation therapy during pregnancy. However, if needed, the drug can be discontinued 24 hours before delivery to minimize the risk of postpartum bleeding.

Nursing implication

- Obtain drug history
- Administration - parenteral- only i.v or deep s.c. (Strictly do not inject i.m)
- Monitor for signs and symptoms of adverse reaction
- Laboratory monitoring typically includes measurements of coagulations, such as activated partial thromboplastin time (aPTT), prothrombin time (PT), plasma heparin concentration (antifactor UFH Xa), whole blood clotting time, activated clotting time, plus a complete blood count (CBC) to monitor platelets and assess for bleeding
- Protamine sulfate (1%) should be kept ready in case of any emergeny due to heparin toxicity or overdose.

DIRECT THROMBIN INHIBITORS

These drugs that exert their anticoagulant effect by directly binding to the active site of thrombin and inhibit thrombin and its downstream effects.

These drugs does not require antithrombin binding to inhibit thrombin, instead they inactivate fibrin-bound thrombin in thrombi and exerts anticoagulant action.

(Table 10.2.4)

DRUGS	MECHANISM OF ACTION	USES	Route of administration
Lepirudin **B**ivalirudin **A**rgatroban **MESSAGE TO STUDENTS** : Formula to remember direct thrombin inhibitors is **"LBA",** you can remember as "**L**ast **B**ench **A**ssociation ", which become **L**epirudin**, B**ivalirudin and **A**rgatroban. The names of first two drugs ends with "rudin", you have to remember Lepi and Bivali, which become **Lepi-**rudin and **Bivali-**rudin. Split the word of last drug and remember as **Arga-tro-ban**	Inactivate fibrin-bound thrombin in thrombi and exerts anticoagulant action.	In thrombosis related to heparin-induced thrombocytopenia (HIT)	**L**epirudin : Parenteral: 50 mg powder for IV injection Bivalirudin : Parenteral: 250 mg per vial Argatroban: Parenteral: 100 mg/ml in 2.5 mL vials

ANTIPLATELET DRUGS / ANTITHROMBOTIC DRUG

- **Non Steroidal Anti-inflammatory Drug:** Aspirin
- ***Phosphodiesterase* inhibitors:** Dipyridamol
- **PTY_1 and PTY_{12} receptor blocker:** Clopidogrel / Ticlopidine
- **Monoclonal antibody:** Abcximab

These drugs interfere with platelet function and hence prevent blood clotting mechanism.

Let us see what is the mechanism that usually takes place in an intact endothelium of blood vessel.

Mechanism in an intact blood vessel

MECHANISM OF PLATELET ACTIVATION

Platelets has various receptors as GP1a, GP1b, GPIIa /IIIb, PGI_2, P2Y1 & $P2Y_{12}$, GP IIb/IIIa, 5HT, ADP and TXA_2 .

- **Collagen** binds to **GP1a** receptors
- **Von Wille brand (VWF)** binds to **GP1b** receptors
- **Prostacyclin** binds to **PGI_2** receptors
- **Serrotonin** binds to **5HT** receptors
- **Thromboxane** binds to **TXA_2** receptors
- **Adenosine diphosphate (ADP)** binds to **P2Y1 & $P2Y_{12}$** receptors
- **Fibrinogen** binds to **GPIIa /IIIb** receptors

VARIOUS MECHANISMS FOR PLATELET AGGREGATION

- Platelet does not bind to intact blood vessel wall
- Prostacyclin will be constantly synthesized from undamaged blood vessel which acts on PGI_2 receptors on platelets which activating adenylate cyclase enzyme which converts ATP to cAMP. Finally the cAMP will be degraded by *phosphodiesterase* enzyme.
- Increased cAMP decreases the synthesis of ADP and TXA_2 from blood vessel.
- Undamaged blood vessel will have intact collagen & von willebrand factors (VWF) **(Fig 10.2.4)**

(Fig 10.2.4)

MECHANISM DURING DAMAGE TO BLOOD VESSEL

- Damage to blood vessel exposes collagen & von willebrand factors (VWF) from endothelium of blood vessel and synthesis of prostacyclin gets inhibited.
- Released collagen from blood vessel binds to GPIa receptor & von willebrand factors (VWF) bind to and GPIb receptors on platelets and activates it.
- Non synthesis of prostacyclin leads to non stimulation of PGI_2 receptor on platelets, non activation of adenylate cyclase and decrease in cAMP. This cause release of ADP and TXA_2 from platelets. **(Fig 10.2.5 & 10.2.6)**

(Fig 10.2.5)

(Fig 10.2.6)

GENERAL MECHANISM AND CLASSIFICATION OF ANTIPLATELET DRUGS

- Inhibition of TXA_2 synthesis by platelet
- Inhibition of phosphodiesterase
- Blocking of $P2Y_1$ & $P2Y_{12}$ Receptors
- Blocking of GPIIb / IIIa receptors

INHIBITION OF TXA_2 SYNTHESIS

ASPIRIN

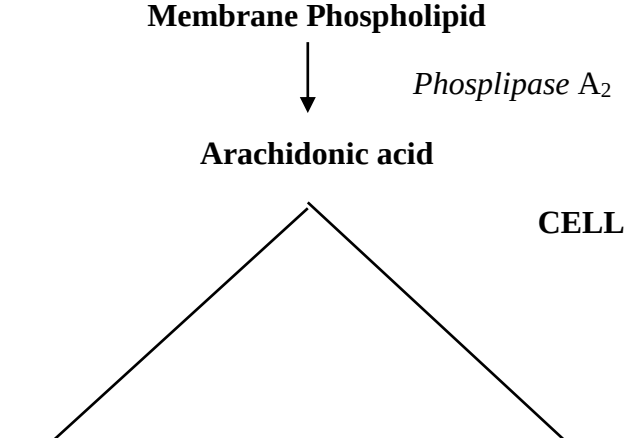
- It belongs to non steroidal anti-inflammatoty drugs (NSAID's)

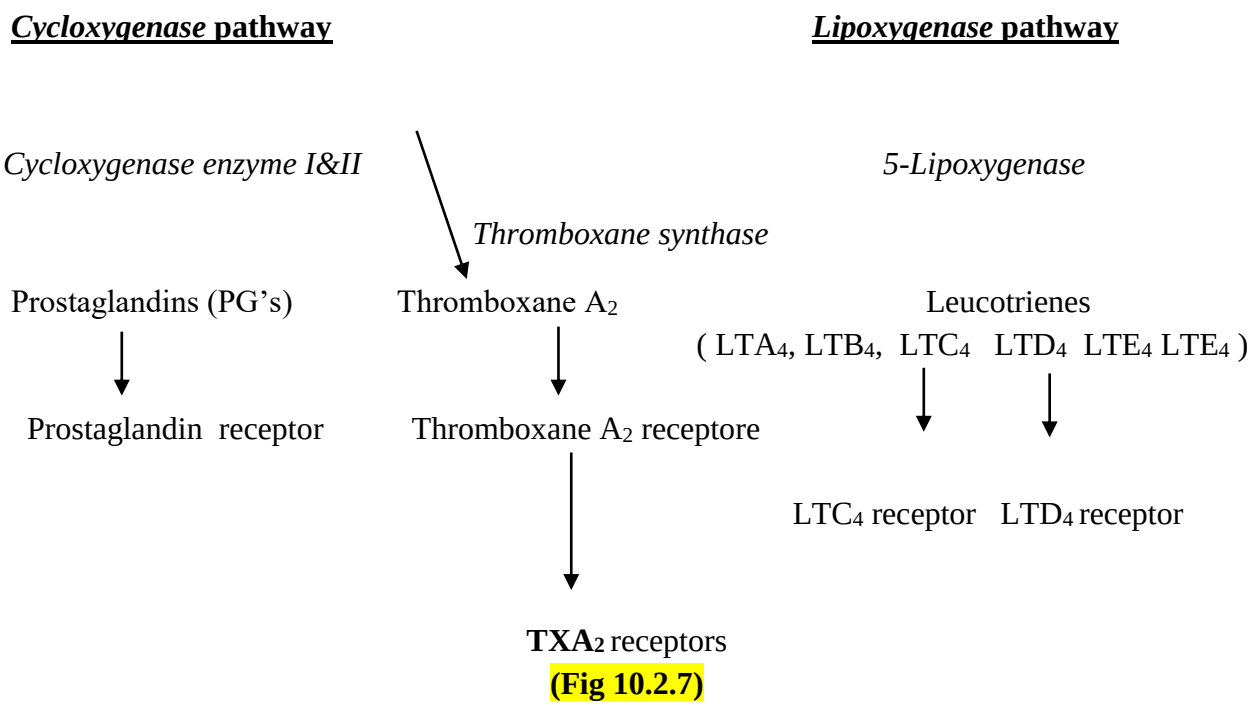
MECHNANISM OF ACTION

- Cycloxygenase (COX) is a key enzyme involved in the synthesis of PG's & thromboxane - A_2 in arachidonic acid pathway.

THROMBOXANE A_2 (TXA_2) SYNTHESIS AND RELEASE **(Fig 10.2.7)**

- Arachidonic acid is formed by the action of *Phosplipase* A_2 *enzyme* on cell membrane phospholipid
- Arachidonic acid undergoes two pathways as *Cycloxygenase* pathway and *Lipoxygenase* pathway.
- Prostaglandins (PG's) and Thromboxane A_2 are formed via *Cycloxygenase* pathway





(Fig 10.2.7)

- *Cycloxygenase* pathway is catalyzed by two isoforms of enzymes called as *Cycloxygenase I* and *Cycloxygenase II* which results in the formation of Prostaglandins (PG's) and Thromboxane A_2

- **Thromboxane A_2** binds to **TXA_2** receptors on platenets and cause platelet activation.
- Aspirin inhibits irreversibly cyclooxygenase (COX) enzyme
- Prevents platelet aggregation / adhesion by interfering TXA_2 synthesis pathway, thus inhibits platelet aggregation (antiplatelet action).

USES

- Prophylaxis angina
- Prophylaxis of myocardial infarction (MI)

During a suspected MI, the recommended dose is 160 mg to 162.5 mg chewed or crushed.

- **To prevent blood clots after total hip replacement surgery**

The recommended dose is 650 mg twice a day started one day before surgery and continued for 14 days after surgery unless otherwise directed by your doctor.

DOSE AND ROUTE OF ADMINISTRATION

Aspirin Oral 50–320 mg/day.

Low dose aspirin

ADVERSE EFFECTS

- Causes and GI irritation & bleeding especially in those who are suffering from peptic ulcer.
- About 2% of population allergic to aspirin
- Anticoagulant effect is undesirable before or after surgery, during pregnancy (especially last trimester), especially in those who are already suffering from defect in clotting mechanism.
- In those <16 yr with virus, flu or chicken pox, aspirin increases risk of Reye's disease (serious (often fatal) with rash, vomiting, and liver damage & neurological disease)

DRUG INTERACTION

- Warfarin and aspirin competes for the same binding site of plasma proteins in which aspirin succeeds and the unbound free warfarin plasma concentration leads to warfarin toxicity.
- Ticlopidine + aspirin: Additive or even synergistic effects

CONTRAINDICATION

- History of drug allergy, Stomach or Intestinal Ulcer, Lactation, Reye's syndrome, Thrombotic Thrombocytopenic Purpura.
- "Aspirin triad" (aspirin sensitivity, nasal polyps, asthma)
- Tinnitus and hearing loss
- Nausea, vomiting, diarrhea, anorexia, heartburn and stomach pains

Nursing implication

- Obtain drug history
- Give the drug with a full glass of water (240 mL), milk, food, or antacid to minimize gastric irritation.
- Enteric-coated tablets dissolve too quickly if administered with milk and should not be crushed or chewed.
- Drugs should be stored at 15°–30° C in airtight container and dry environment

- Monitor for loss of tolerance to aspirin. The reaction is nonimmunologic; symptoms usually occur 15 min to 3 h after ingestion: profuse rhinorrhea, erythema, nausea, vomiting, intestinal cramps, diarrhea.
- Lab tests: Monitor for all blood parameters
- Monitor the diabetic patient carefully for need to adjust insulin dose. High doses of aspirin are particularly prone to hypoglycemia.
- Monitor for salicylate toxicity. In adults, a sensation of fullness in the ears, tinnitus, and decreased or muffled hearing are the most frequent symptoms associated with chronic salicylate overdosage.
- Watch for manifestation of salicylate toxicity by hyperventilation, agitation, mental confusion, or other behavioral changes, drowsiness, lethargy, sweating, and constipation.
- **Note:** Potential for toxicity is high in older adults and patients with asthma, nasal polyps, perennial vasomotor rhinitis, hay fever, or chronic urticaria.

***PHOSPHODIESTERASE* INHIBITORS**
DIPYRIDAMOL

- It is a *phosphodiesterase* inhibitors

MECHNANISM OF ACTION

- We know that prostacyclin will be constantly synthesized from undamaged blood vessel which acts on PGI_2 receptors on platelets which activating adenylate cyclase enzyme which converts ATP to cAMP. Finally the cAMP will be degraded by *phosphodiesterase* enzyme.
- Dipyridamol inhibits *phosphodiesterase* enzyme and inhibits degradation of cAMP in platelets.
- Increased cAMP in platelets will inhibits activation of platelets exhibiting anti-platelet action **(Fig 10.2.8)**

(Fig 10.2.8)

USES

- In combination with aspirin to prevent cerebrovascular ischemia.
- In combination with warfarin for primary prophylaxis of thromboemboli in patients with prosthetic heart valves (defect in tricuspid, mitral valves pulmonary or aortic valves).
- A combination of dipyridamole with aspirin is used for secondary prophylaxis of cerebrovascular disease.

DOSE AND ROUTE OF ADMINISTRATION

Oral: 25, 50, 75 mg tablets

Oral combination product: 200 mg extended-release dipyridamole plus 25 mg aspirin

ADVERSE EFFECTS

Coronary steal phenomenon: Reduce perfusion of blood of ischemic areas and may aggravate angina symptoms.

DRUG INTERACTION

Adenosine effect will be increased by Dipyridamol

Dipyridamole and cilostazol are additional antiplatelet drugs.

CONTRAINDICATION

Hypersensitivity to dipyridamole and any of the other components

Nursing implication

- Monitor blood pressure and pulse before and during therapy
- LAB CONSIDERATION: monitoring of bleeding time throughout therapy
- Observe for patient complaining of acute pain
- Instruct patient to take at the drug at instructed regular intervals. If a dose is missed, advice to take as soon as remembered unless next dose is within 4 hours and do not double doses
- Advice to avoid use of alcohol (potentiate hypotension) and tobacco (vasoconstriction)

PTY_1 AND PTY_{12} RECEPTOR BLOCKER
CLOPIDOGREL / TICLOPIDINE

These are **PTY_1** and **PTY_{12}** receptor blocker

MESSAGE TO STUDENTS : Formula to remember **PTY_1** and **PTY_{12}** receptor blocker is **"CT",** you just remember as **" Crucial Time".** Split the name of the word and remember as **Clo-pi-dog-rel** and **Ticlo-pi-dine.**

MECHANISM OF ACTION

- We already know that ADP released due to platelet activation will act on **PTY_1** and **PTY_{12}** receptor present on other platelets favoring for blood clot.

- Clopidogrel / Ticlopidine are **PTY_1** and **PTY_{12}** receptor blocker, hence prevent the action of ADP present on other platelets and thus prevent blood clot. **(Fig 10.2.9)**

(Fig 10.2.9)

USES

- Unstable angina

In combination with aspirin for following indications

- Prophylaxis angina
- Prophylaxis of myocardial infarction (MI)
- To prevent blood clots after total hip replacement surgery

DOSE AND ROUTE OF ADMINISTRATION

Clopidogrel : Initial dose is 300 mg followed by a maintenance dose of 75 mg/d

Ticlopidine: 250 mg twice daily

ADVERSE EFFECTS

Clopidogrel : Severe allergic reactions (rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue, unusual hoarseness of voice), black, tarry

stools and in some patients may lead to thrombotic thrombocytopenic purpura. But less incidence of neutropenia or leucopenia.

Ticlopidine:

Nausea, dyspepsia, diarrhea, hemorrhage and neutropenia or leukopenia

DRUG INTERACTION

- Ticlopidine potentiates the effect of aspirin or other NSAIDs on platelet aggregation.
- Antacids decreases plasma levels of ticlopidine
- Atorvastatin and omeprazole competitively inhibit CYP enzyme induced activation of clopidogrel, reducing clopidogrel responsiveness.

CONTRAINDICATION

Clopidogrel

- Allergic to any ingredient in clopidogrel
- Patient suffering from active bleeding problem (eg, bleeding stomach ulcer, bleeding in the brain)

Ticlopidine

Hypersensitivity, hemorrhagic diathesis, gastrointestinal ulcers, liver dysfunction, presence of hematological disorders

Nursing implication

- Assess history of allergy to the drug
- Obtain history about pregnancy, lactation, bleeding disorders, recent surgery, hepatic impairment, peptic ulcer
- Advice patient to take medicine daily as prescribed.
- Advice patient to report if they experience dizziness and light-headedness
- Report to doctor about appearance of skin rash, chest pain, fainting, severe headache and abnormal bleeding.

GPIIb /IIIa RECEPTOR BLOCKERS

TIROFIBAN / EPTIFIBATIDE / ABCIXIMAB

- Tirofiban is a smaller molecule analog of fibrinogen
- Eptifibatide is an analog of fibrinogen
- Abciximab is a humanized monoclonal antibody

MESSAGE TO STUDENTS : Formula to remember **GPIIb /IIIa** receptor blockers is **"TEA",** just remember the drink "**TEA"** which you used to drink in morning as bed tea, which become **T**irofiban, **E**ptifibatide and **A**bciximab.

MECHANISM OF ACTION

- We already know that during clotting process the fibrinogen binds to GP IIb / IIIa receptors on other platelets.
- Abiciximab is a monoclonal antibody developed against GP IIb / IIIa receptors.
- Blocking of GP IIb / IIIa and inhibit binding of fibrinogen to GP IIb / IIIa → inhibit platelet aggregation. **(Fig 10.2.10)**

(Fig 10.2.10)

USES

In percutaneous coronary intervention and in acute coronary

DOSE AND ROUTE OF ADMINISTRATION

- Tirofiban: Intravenously 25 mcg/kg over 3 minutes and then 0.15 mcg/kg/min for up to 18 hours.
- Eptifibatide : i.v. loading dose of 180 µg/kg over 1 to 2 minutes followed by continuous i.v.-infusion of 2 µg/kg per minute
- Abciximab: i.v bolus of 0.25 mg/kg plus a 0.125 mcg/kg/min infusion (to a maximum of 10 mcg/min) for 12 hours

ADVERSE EFFECTS

- Anaphylaxis

- Bleeding
- Rarely thrombocytopenia may occur in patients treated with abciximab.

DRUG INTERACTION

GPIIb /IIIa receptor blockers with other anticoagulant may increase bleeding tendency.

CONTRAINDICATION

History of drug allergy

Nursing implication

- Assess history of allergy to the drug
- Obtain history about pregnancy, lactation, bleeding disorders, recent surgery, hepatic impairment, peptic ulcer
- Advice patient to take medicine daily as prescribed.
- Advice patient to report if they experience dizziness and light-headedness
- Report to doctor about appearance of skin rash, chest pain, fainting, severe headache and abnormal bleeding.

FIBRINOLYTICS / THROMBOLYTICS AND ANTI-FIBRINOLYTICS

First let us know how the clot breaks

After the formation of clot, a specialized mechanism called as **"Fibrinolytic system"**come into play to break or lyse the clot.

FIBRINOLYTIC SYSTEM

- During breakdown of clot the intrinsic activators like Factor XIIa (12a), Tissue plasminogen activator (t-PA), Kallikrein released from vessel wall converts Plasminogen (inactive form) to Plasmin (active form)
- Activated plasmin breaks down fibrin clots and results in fibrinolysis. **(Fig 10.2.11)**

(Fig 10.2.12)

FIBRINOLYTICS / THROMBOLYTICS

DRUG USED

- Streptokinase
- Urokinase
- Tenecteplase
- Anistreplase
- Reteplase
- Alteplase

MESSAGE TO STUDENTS : Formula to remember fibrinolytics is "SU-TARA", which becomes Streptokinase , Urokinase , Tenecteplase, Anistreplase, Reteplase and Alteplase

- Streptokinase : It is a protein (but not an enzyme in itself) synthesized by streptococci bacteria
- **Urokinase** is a human enzyme synthesized by the kidney that directly converts plasminogen to active plasmin.
- Tenecteplase, Anistreplase, Alteplase and Reteplase are recombinant human tissue plasminogen activators (t-PA).

MECHANISM OF ACTION

- Fibrinolytics helps in activation of Plasminogen (inactive form) to Plasmin (active form)
- Activated plasmin breaks down fibrin clots and results in fibrinolysis. **(Fig 10.2.12)**

(Fig 10.2.12)

USES

- In multiple pulmonary emboli
- Central deep venous thrombosis

- Acute myocardial infarction
- In patients with acute stroke symptoms

DOSE AND ROUTE OF ADMINISTRATION

Streptokinase: intravenous infusion of a loading dose of 250,000 units, followed by 100,000 units/h for 24–72 hours.

Urokinase : Loading dose of 300,000 units given over 10 minutes and a maintenance dose of 300,000 units/h for 12 hours.

Tenecteplase : Single intravenous bolus of 0.5 mg/kg.

Anistreplase: Single intravenous injection of 30 units over 3–5 minutes.

Reteplase : Two intravenous bolus injections of 10 units each, separated by 30 minutes.

Alteplase: Intravenous infusion of 60 mg over the first hour and then 40 mg at a rate of 20 mg/h.

ADVERSE EFFECTS

Patients with antistreptococcal antibodies can develop fever and allergic reactions especially to streptokinase.

DRUG INTERACTION

Aspirin + Fibrinolytics leads to excessive bleeding rates

CONTRAINDICATION

In patients suffering from active peptic ulcer, a bleeding disorder, active lung disease, severe liver disease, or acute pancreatitis, or to those who have recently had a stroke, haemorrhage, or injury, or who have recently undergone surgery (including tooth extraction).

Nursing implication

- Assess history of allergy to the drug
- Obtain history about pregnancy, lactation, bleeding disorders, recent surgery, hepatic impairment, peptic ulcer
- Advice patient to take medicine daily as prescribed.
- Advice patient to report if they experience dizziness and light-headedness

- Report to doctor about appearance of skin rash, chest pain, fainting, severe headache and abnormal bleeding.
- Monitor for signs and symptoms of bleeding problems, such as bleeding gums or presence of blood in stool.
- Reduce the number of punctures and apply pressure to puncture sites, closely watch for any bleeding signs.
- The patient and family should be educated about necessary precautions when taking anticoagulants, such as using as a soft toothbrush and an electric razor, returning for routine laboratory tests etc

ANTI-FIBRINOLYTICS / FIBRINOLYTIC INHIBITORS

DRUG USED

- Epsilon amino-caproic acid (EACA)
- Tranexaemic acid

MECHANISM OF ACTION

- Anti-fibrinolytic / Fibrinolytic Inhibitors are the drugs bind to both plasminogen and plasmin and prevent activation of Plasminogen (inactive form) to Plasmin (active form) and hence stabilizes the clot. **(Fig 10.2.13)**

(Fig 10.2.13)

USES

- In overdose of fibrinolytics
- To prevent recurrent subarechnoid and g.i bleeding
- To prevent traumatic and surgical bleeding etc

DOSE AND ROUTE OF ADMINISTRATION

- Epsilon amino-caproic acid (EACA): oral dosage of EACA is 6 g four times a day. When the drug is administered intravenously, a 5 g loading dose should be infused over 30 minutes to avoid hypotension.
- Tranexamic acid: orally with a 15 mg/kg loading dose followed by 30 mg/kg every 6 hours.

ADVERSE EFFECTS

Intravascular thrombosis, hypotension, myopathy, abdominal discomfort, diarrhea, and nasal stuffiness.

DRUG INTERACTION

None reported

CONTRAINDICATION

In patients with disseminated intravascular coagulation or genitourinary bleeding of the upper tract, eg, kidney and ureters as it may lead to excess of bleeding.

Nursing implication

- Obtain patient history, medication history and allergies
- Obtain baseline vital signs and interpret laboratory values
- Obtain history of abnormal bleeding conditions

COAGULANTS OR PROCOAGULANTS

The use of adsorbent chemicals, such as zeolites, and other hemostatic agents are also used for sealing severe injuries quickly (such as in traumatic bleeding secondary to gunshot wounds). Thrombin and fibrin glue are used surgically to treat bleeding and to thrombose aneurysms.

Desmopressin is used to improve platelet function by activating arginine vasopressin receptor 1A.

Coagulation factor concentrates are used to treat hemophilia, to reverse the effects of anticoagulants, and to treat bleeding in patients with impaired coagulation factor synthesis or increased consumption. Prothrombin complex concentrate, cryoprecipitate and fresh frozen plasma are commonly used coagulation factor products. Recombinant activated human factor VII is increasingly popular in the treatment of major bleeding.

(Table 10.2.5)

DRUGS	MECHANISM OF ACTION	USES
Prothrombin complex concentrate (combination of blood clotting factors II, VII, IX and X, as well as protein C and S)	Activates blood coagulation mechanism	To reverse the effect of warfarin and other coumarin anti-coagulants. In deficiency clotting factors, either due to congenital or due to liver disease and hemophilia.

Fibrin glue (made up of fibrinogen (lyophilised pooled human concentrate) and thrombin (bovine, which is reconstituted with calcium chloride)[]	Fibrin arrest the bleed and Thrombin is an enzyme and converts fibrinogen into fibrin monomers between 10 and 60 seconds giving rise to a three dimensional gel	Used in case repairing dura tears, bronchial fistulas and for achieving hemostasis after spleen and liver trauma
Fresh frozen plasma with coagulation factor products	Hemostatic	Coagulation factor deficiencies and active bleeding, or who are about to undergo an invasive procedure. Deficiency of clotting factor either congenital or acquired like secondary to liver disease, warfarin anticoagulation, disseminated intravascular coagulation, or massive replacement with red blood cells and crystalloid/colloid solutions
Recombinant activated human factor VII	Activates of the extrinsic pathway of blood coagulation	hemophilia type A and B
Coagulation factor concentrates (prothrombin complexes, Factor XIII, and Factor VII)	Reverses the effects of anticoagulants	Excessive bleeding due to trauma, liver disease, and oral anticoagulant toxicity
Cryoprecipitate	Activates blood coagulation mechanism	Haemophilia Von Willebrands's disease (Used for emergency back up when factor concentrates are not available.)
Desmopressin	Activates arginine vasopressin receptor 1A and improves platelet function	Mild to moderate hemophilia to help increase clotting factors when they have certain medical or dental procedures done.

STYPTICS / LOCAL HAEMOSTATICS

These are the drugs that act by adsorption (physical binding) or by contracting the tissue or by vasoconstriction to seal injury resulting in stoppage of bleeding from local or peripheral sites.

(Table 10.2.6)

DRUGS	MECHANISM OF ACTION	USES

Gelatin sponge or Foam of gelatin or	A mesh or strip like material, when applied to open wound activates clotting factors at local sites.	Bleeding from surface wounds
Oxidized regenerated cellulose	A mesh or strip like material, when applied to open wound activates clotting factors at local sites.	Bleeding gums, bleeding tooth socket, or epistaxis (bleeding from nose)
Astringents	Precipitates surface proteins and arrest bleeding	Bleeding gums, bleeding piles etc
Thrombin	Applied as dry powder which acts by adsorption (physical binding))	To arrest bleeding from surface wounds
Vasoconstrictors **(Adrenaline)**	By acting on α_1 receptors on blood vessel, it cause vasoconstriction and arrest bleeding from local sites	Cotton gauge soaked in dilute solution of adrenaline can be pressed against bleeding sites like tooth sockets, nostrils etc.
Zeolites (contains a calcium-loaded form of zeolite found in kaolin clay)	A mesh or strip like material, when applied to open wound activates clotting factors at local sites.	To arrest bleeding from surface wounds

CHAPTER 10.3

ANTIHYPERTENSIVES AND VASODILATORS

Hypertension is increase in blood pressure more than normal. Normal blood pressure ranges between 120-140 / 80-90 mmHg. So blood pressure >140/90mm Hg recorded on three different occasion can be considered as hypertension.

TYPES AND CAUSES OF HYPERTENSION

Essential hypertension: Patients in whom no specific cause of hypertension can be found are said to be having essential hypertension. It is believed that the increase in blood pressure in this setting is essential for that particular person and hence the name as **Essential hypertension.**

Non Essential hypertension

Here there will be increase in blood pressure due to other causes like pheochromocytoma (tumor of adrenal gland), hyperaldersteronism, hyperthyroidism etc

PATHOLOGY **(Fig. 10.3.1)**

Increased in blood pressure involves central nervous system (CNS) including ganglion, cardiovascular system (CVS) and renal system.

Role of CNS and ganglion: Central nervous system sends sympathetic outflow which stimulates peripheral sympathetic ganglia that releases catecholamines (especially adrenaline and noradrenaline).

Role of CVS: Increased activity of sympathetic nervous system leads to increased activity of catecholamines (especially adrenaline and noradrenaline) on its adrenergic receptors (α & β receptors) leading to increased heart rate and peripheral vasoconstriction resulting in increased blood pressure.

Role of renal system: Increased activity of sympathetic nervous system leads to simulation of adrenal gland present on upper pole of kidneys, thus activating Renin-angiotensin-system (RAS) or Renin-angiotensin-aldosterone mechanism.

- Renin released from kidney converts Angiotensinogen to Angiotensin I
- *Angiotensin converting enzyme* converts Angiotensin I to Angiotensin II
- Angiotensin II will act on ATI receptors present on vascular smooth muscle and results in vascular smooth muscle contraction, thus increasing blood pressure.
- Angiotensin II action on adrenal medulla releases Aldosterone (mineralocorticoid), thus leading to sodium and water retention, increases plasma volume and contributes for increased blood pressure.

(Fig. 10.3.1)

Aim of the treatment of hypertension is as follows

- Reducing central sympathetic outflow
- Blocking the ganglion stimulation
- Causing increased excretion of sodium and water via urine
- Causing vasodilatation
- Blocking the action of catecholamines on heart and vascular smooth muscle
- Inhibition of activation of Renin-angiotensin-system (RAS)

For remembering purpose, let us remember and study the drugs by using formula

Antihypertensive drugs classification can be alphabetically remembered as **A, B, C, D & V,** you can remember a movie named "**ABCD"** which means **"A**ny**B**ody **C**an **D**ance**"** and just add **V** at last. Now add **3** to **A** and **2** to **C** and remember as **A^3, B, C^2, D &V.**

A^3:

- **A**ngiotensin converting enzyme inhibitors : **C**aptopril and **E**nalapril
- **A**ngiotensin I receptor blockers: **T**elmisartan **L**osartan **I**rbesartan **and C**andesartan
- **A**lpha (α) blockers : **P**razosin**, T**erazosin **and D**oxazosin

ADRENERGIC NEURON BLOCKERS OR GANGLION BLOCKERS:

Guanethidine

B:

B BLOCKERS OR B RECEPTOR ANTAGONIST:

- Propranolol (Non selective β blocker)
- Metoprolol
- Atenolol } Selective β_1 blocker
- Bisoprolol

C^2:

- **C**alcium channel blockers (CCBs)
- **C**entral sympatholytics

D : Diuretics

- **Loop diuretics / high efficacy or high ceiling diuretics: F**urosemide and **T**orsemide
- **Thiazides diuretics : H**ydrochlorothiazide and **H**ydroflumethiazide
- **Potassium (k^+) sparing diuretics : Aldosterone antagonist: S**pironolactone **and Sodium channel blockers: A**miloride and **T**riampterene

V: Vasodilators

- **Selective arteriolar dilators : H**ydralazine, **M**inoxidil, **D**iazoxide and **F**enoldopam
- **Venous dilators: N**itrates
- **Arterial and venous dilators : S**odium nitroprusside

A^4

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACE INHIBITORS)

DRUG USED

Captopril

Enalapril

MESSAGE TO STUDENTS: Formula to remember the drugs used as angiotensin-converting enzyme inhibitors (ACE inhibitors) as **"CE",** you can remember as **"C**hemical **E**ngineer**",** which becomes **C**aptopril and **E**nalapril. Here the names of both the drugs ends with common words as **"pril",** you have to remember "Capto" and "Enala". Now remember as "**Capto-** pril" and "**Enala-** pril".

Other drugs used as ACE inhibitors are **Rami**-pril **, Lisino**-pril, **Fosino**-pril **, Benaze**-pril, **Moexi**-pril, **Perindo**-pril**, Quina**-pril, , and **Trandola**-pril.

Note: Here also the name of all the drugs ends with a common word as **"pril"**

MECHANISM OF ACTION

Already we know the role of angiotensin converting enzyme for increase of blood pressure

- Following factors stimulate **Renin** release from the kidney

    a) Reduced renal arterial pressure
    b) Sympathetic stimulation
    c) Reduced sodium delivery or
    d) Increased sodium concentration at the distal renal tubule

- Renin acts upon inactive angiotensinogen to angiotensin I.

- Angiotensin I will be then converted, by endothelial enzyme *Angiotensin converting enzyme* (ACE), to angiotensin II

- Angiotensin II acts on AT1 receptor on blood vessel and leads to has vasoconstrictor

- Angiotensin II acts on adrenal gland and increases aldosterone secretion which retains sodium and water.

- Both vasoconstriction and increased sodium and water leads to increased blood pressure. **(Fig. 10.3.1)**

- *Angiotensin converting enzyme* inhibitors inhibits *Angiotensin converting enzyme* and prevent the conversion of angiotensin I to angiotensin II, thus it results in vasodilatation and reduces blood pressure

It also increases GFR leading to increased excretion of sodium and water. **(Fig. 10.3.2)**

(Fig. 10.3.2)

USES

Hypertension

OTHER USES

- Congestive heart failure

- Myocardial infarction

DOSE AND ROUTE OF ADMINISTRATION

Captopril : Oral: 12.5, 25, 50, 100 mg tablets

Enalapril : Oral: 2.5, 5, 10, 20 mg tablets

ADVERSE EFFECTS

Dry Cough & Angioedema (due to inhibition of bradykinin degradation) **(Fig. 10.3.4)**

(Fig. 10.3.4)

Skin Rash

- Hypotension : Orthostatic or postural hypotension
- Hyperkalemia
- Acute Renal Failure
- Fetopathic

- Proteinuria

DRUG INTERACTION

- Antacids reduce the oral bioavailability of ACE inhibitors

- K^{+}-sparing diuretics and K+ supplements may exacerbate ACE inhibitor–induced hyperkalemia.

CONTRAINDICATION

- In second trimester of pregnancy

- Bilateral renal artery stenosis.

Nursing Implication

- Obtain a complete health history of the patient including recent cardiac events and any incidence of angioedema, allergies, drug history, and possible drug interactions.
- Always check blood pressure before starting antihypertensive drug for the first time.
- Obtain baseline ECG and vital signs.
- Assess neurological status and level of consciousness.
- Obtain blood and urine specimens for laboratory analysis.
- About the first-dose phenomenon and reassure that this effect diminishes with continued therapy.
- To immediately report feelings of faintness because rapid reduction in blood pressure can cause changes in consciousness.
- To rest in the supine position beginning 1 hour after administration and for 3 to 4 hours after the first dose.

ANGIOTENSIN RECEPTOR ANTAGONISTS (AT$_1$ RECEPTOR BLOCKER (ARBs) OR AT$_1$ RECEPTOR ANTAGONIST)

DRUG USED

Telmisartan
Losartan
Irbesartan
Candesartan

MESSAGE TO STUDENTS: Remember the drugs used as angiotensin receptor blockers or antagonist or AT_1 receptor antagonist or ARBs is **"Tell-me - LIC",** you can remember as "**Tel**–**mi**- **L**ife **I**nsurance **C**orporation", which becomes **T**elmisartan, **L**osartan , **I**rbesartan and **C**andesartan. The names of the drugs ends with common words as "sartan", you have to remember Losa, Irbe and Cande, which becomes **Telmi**-sartan**, Losa**-sartan, **Irbe**-sartan and **Cande-**sartan.

Other drugs used as angiotensin receptor blockers or antagonist or AT_1 receptor antagonist or ARBs are **val-**sartan and **Epro**-sartan.

MECHANISM OF ACTION

- We already know that Angiotensin II acts on AT1 receptor on blood vessel and leads to has vasoconstrictor.

- Angiotensin receptor antagonists (AT1 antagonist or blocker) blocks Angiotensin receptor and inhibits the action of Angiotensin II acts on AT_1 receptor on vascular smooth muscle.

- It results in vasodilatation and reduces blood pressure.

It also increases GFR due to decreased aldosterone secretion and renal vasodilatation leading to increased excretion of sodium and water. **(Fig. 10.3.4)**

-

(Fig. 10.3.4)

USES

Hypertension in those who experience dry cough & angioedema with ACE inhibitors

OTHER USES

- Congestive heart failure

- Myocardial infarction

DOSE AND ROUTE OF ADMINISTRATION

Telmisartan Oral: 20, 40, 80 mg tablets

Losartan Oral: 25, 50, 100 mg tablets

Irbesartan Oral; 75, 150, 300 mg tablets

Candesartan Oral: 4, 8, 16, 32 mg tablets

ADVERSE EFFECTS

- Teratogenic Potential
- Hypotension
- Oliguria
- Progressive Azotemia (elevation of blood urea nitrogen (BUN) and serum creatinine levels.)
- Acute Renal Failure.
- Hyperkalemia

DRUG INTERACTION

- K^{+}-sparing diuretics and K+ supplements may exacerbate ARBs induced hyperkalemia.

CONTRAINDICATION

- In second trimester of pregnancy

- Bilateral renal artery stenosis.

Nursing Implication

- Always check blood pressure before starting antihypertensive drug for the first time.
- Monitor Blood Urea Nitrogen
- Monitor creatinine and electrolytes
- Tell the patients to report edema in feet and legs daily.
- Monitor hydration status.

ALPHA (α) BLOCKERS

DRUGS USED

Prazosin
Terazosin
Doxazosin

MESSAGE TO STUDENTS: Remember the drugs used as **"PTD",** you can remember as "Private Tuition Department", which becomes **P**razosin**, T**erazosin and **D**oxazosin. Here the names of all the drugs ends with common word as **"Zosin",** you have to remember Pra, Tera and Doxa, which becomes **Pra**-zosin**, Tera**-zosin and **Doxa**-zosin.

Other drugs considered under α blockers are **Tamsu**-losin and **Alfu**-zosin

MECHANISM OF ACTION

- We already know that increased activity of sympathetic nervous system leads to increased activity of catecholamines (especially adrenaline and noradrenaline) on its adrenergic receptors especially α_1 receptors present on smooth vessel of the blood vessel and peripheral vasoconstriction resulting in increased blood pressure.

Selective α_1 blocker blocks α_1 receptors present on smooth vessel of the blood vessel leads to peripheral vasodilatation resulting in decreased blood pressure. **(Fig. 10.3.5)**

(Fig. 10.3.5)

USES

Hypertension

DOSE AND ROUTE OF ADMINISTRATION

Prazosin Oral: 1, 2, 5 mg capsules
Terazosin Oral: 1, 2, 5, 10 mg tablets, capsules
Doxazosin Oral: 1, 2, 4, 8 mg tablets

ADVERSE EFFECTS

Dizziness, lightheadedness, or fainting when rising from a lying or sitting posture (known as orthostatic hypotension or postural hypotension). For this reason, it is generally recommended that alpha blockers should be taken at bedtime. Additionally, the risk of first dose phenomenon may be reduced by starting at a low dose and titrating upwards as needed.

E.g. Even though the starting dose of prazosin is 1mg, you can start with 0.5mg at bed time and gradually increase the dose based on the response.

DRUG INTERACTION

Alpha blockers + Vasodilators: Profound hypotension

CONTRAINDICATION

Urinary incontinence

Nursing Implication

- Obtain drug history
- Always check blood pressure before giving antihypertensive drug for the first time.
- Advice patient to change positions slowly to prevent or minimize postural hypotension
- Advice the patient to take the drug at bed time and not to get up suddenly after taking the drug.
- Advice patient to avoid caffeine as it causes excessive irritability
- Advice patient to avoid alcohol ingestion and hazardous activities until blood levels become stable
- Advice patient to notify their physician if palpitations, dyspnea, nausea or vomiting occurs

ADRENERGIC NEURON BLOCKERS OR GANGLION BLOCKERS

DRUGS USED

Guanethidine

MECHANISM OF ACTION

- Sympathetic and parasympathetic ganglions have nicotinic N_N cholinoceptors.

- Stimulation of Sympathetic ganglion releases catecholamines which acts on adrenergic receptors and hence cause increase in blood pressure.

- Guanethidine is transported across the sympathetic nerve membrane by the same mechanism that transports norepinephrine itself (uptake 1)

- Once guanethidine has entered the nerve, it is concentrated in transmitter vesicles, where it replaces. norepinephrine.

- Because it replaces norepinephrine, the drug causes a gradual depletion of norepinephrine stores in the nerve ending.

- Hence the sympathetic effects of catecholamines gets reduced and results in decrease in blood pressure.

USES

Hypertension

DOSE AND ROUTE OF ADMINISTRATION

Guanethidine Oral: 10, 25 mg tablets

ADVERSE EFFECTS

- Postural hypotension
- Delayed or retrograde ejaculation (into the bladder)
- Diarrhea

DRUG INTERACTION

Cocaine, amphetamine, tricyclic antidepressants, phenothiazines, and phenoxybenzamine either block the catecholamine uptake process or displace amines from the nerve terminal and decrease effect of Guanethidine

CONTRAINDICATION

- Phaeochromocytoma
- Congestive heart failure
- Narrow-angle glaucoma
- Hypersensitivity.

Nursing Implication

- Obtain drug history
- Always check blood pressure before starting antihypertensive drug for the first time.
- Advice patient to discontinue drug if diarrhea is severe.
- Advice patient to discontinue guanethidine therapy at least 2 wk prior to surgery to reduce the possibility of vascular collapse and cardiac arrest during anesthesia.
- It is better to decrease dosage during fever, which decreases drug requirements.
- Monitor patient for orthostatic hypotension, which is most marked in the morning and is accentuated by hot weather, alcohol, exercise etc
- Monitor for all necessary parameter during course of the therapy

β BLOCKERS
OR
β RECEPTOR ANTAGONIST

- Propranolol (Non selective β blocker)

- Metoprolol
- Atenolol
- Bisoprolol

} Selective β_1 blocker

MESSAGE TO STUDENTS: Formula to remember the drugs used as β blockers or β receptor antagonist is "**P.MAB",** you can remember as **"P**lease **M**arry **A B**lind**",** which becomes **P**ropranolol , **M**etoprolol, **A**tenolol and **B**isoprolol. Here the names of all the drugs ends with common word **"olol",** you have to remember **Propran, Metopr, Aten** and **Biso**, which becomes **Propran**-olol , **Metopr**-olol**, Aten**-olol and **Biso**-prolol

MECHANISM OF ACTION (Fig. 10.3.6)

- **Heart:** Stimulation of β_1 receptors on SA node of the heart will increase heart rate and force of contraction.

  So, β blockers blocks β_1 receptors on SA node of the heart and hence will decrease cardiac contractility (negative inotropic effect) and heart rate (negative chronotropic effect)

- **Kidney:** Blockade of beta1-receptors inhibits the release of renin from juxta-glomerular cells and thereby reduces the activity of the renin-angiotensin-aldosterone system.

- **Central and peripheral nervous system:** Blockade of beta-receptors in the brainstem and prejunctional beta-receptors in the periphery inhibits the release of neurotransmitters and decreases sympathetic nervous system activity.

(Fig. 10.3.6)

USES

Hypertension

DOSE AND ROUTE OF ADMINISTRATION

Propranolol Oral: 10, 20, 40, 60, 80, 90 mg tablets; 4, 8, 80 mg/mL solutions, Oral sustained release: 60, 80, 120, 160 mg capsules and Parenteral: 1 mg/mL for injection

Metoprolol Oral: 50, 100 mg tablets, Oral sustained-release: 25, 50, 100, 200 mg tablets and Parenteral: 1 mg/mL for injection.

Atenolol Oral: 25, 50, 100 mg tablets and Parenteral: 0.5 mg/mL for IV injection

Bisoprolol Oral: 5, 10 mg tablets

ADVERSE EFFECTS

- Bradycardia caused by β blockers may cause life-threatening bradyarrhythmias in patients with partial or complete AV conduction defects.
- Fatigue, sleep disturbances (including insomnia and nightmares), and depression.
- Sudden or abrupt withdraw of β blockers may lead to rebound hypertension
- Non selective β blocker like propranolol can worsen asthma by blocking β_2 in bronchial smooth muscle causing bronchoconstriction.

DRUG INTERACTION

- **Cimetidine + β -blockers:** Decreased metabolism of β -blockers that are cleared primarily by the liver
- Aluminum salts, cholestyramine, and colestipol may decrease absorption of b blockers.

CONTRAINDICATION

Second or Third Degree Heart Block

Bronchial asthma is a contraindication for Non selective β blockers (E.g. Propranolol)

Nursing Implication

- Obtain drug history

- Always check blood pressure before starting antihypertensive drug for the first time, if BP is below 90 systolic or 60 beats per minute (BPM) hold the drug and notify doctor.
- When patient are taking beta blockers, it is also very important to monitor the changes in lab values such as (protien, BUN and creatinine) which can indicate nephrotic syndrome.
- Advice patient NOT STOP TAKING DRUG SUDDENLY. Doing so may cause tachycardia, dysrythmias, elevated BP, angina and MI.
- If patient is on extended release forms of the drug, advice not to be crushed and taken.

C^2

CALCIUM CHANNEL BLOCKERS (CCBs)

Non-dihydropyridines

- **Phenylalkylamine : V**erapamil
- **Benzothiazepine : D**iltiazem

Dihydropyridine

- **F**elodipine
- **I**sradipine
- **A**mlodipine
- **N**icardipine
- **N**ifedipine
- **N**isoldipine

MESSAGE TO STUDENTS: Formula to remember the drug used as calcium channel blockers is **V.D. FIAN^3,** you can remember as **"V**ictory **D**ay **F**or **I**ndia **A**fter **N**oble^3**".** Under **Phenylalkylamines** remember the drug **"V"** by splitting the word as "**Vera-pa-mil"** and under **benzothiazepine,** remember the drug **"D"** by splitting the word as **"Dil-tia-zem".**

Under **Dihydropyridine** , the names of all the drugs ends with a common word **"dipine",** you have to remember **F**elo, **I**sra**, A**mlo**, N**icar**, N**ife and **N**isol, which becomes **Felo**-dipine**, Isra**-dipine**, Amlo**-dipine**, Nicar**-dipine**, Nife-**dipine and **Nisol**-dipine

MECHANISM OF ACTION (Fig. 10.3.7)

Activation of calcium channel on SA node of the heart leads to increase in force of contraction and also increases electrical conduction resulting in increased heart rate. Similarly activation of calcium channels on blood vessel leads to vasoconstriction.

- Calcium channel blockers blocks calcium channels on vascular smooth muscle they reduce contraction of the arteries and cause an increase in arterial diameter, a phenomenon called vasodilation (CCBs do not work on venous smooth muscle)

- Calcium channel blockers blocks calcium channels on cardiac muscles (myocardium), they reduce the force of contraction of the heart

- Calcium channel blockers blocks calcium channels on SA node, thus slowing down the conduction of electrical activity within the heart, they slow down the heart beat.

(Fig. 10.3.7)

USES

Hypertension

DOSE AND ROUTE OF ADMINISTRATION

Verapamil Oral: 40, 80, 120 mg tablets, Oral sustained-release and 120, 180, 240 mg tablets; 100, 120, 180, 200, 240, 300 mg capsules and Parenteral: 2.5 mg/mL for injection

Diltiazem Oral: 30, 60, 90, 120 mg tablets , Oral sustained-release 60, 90, 120, 180, 240, 300, 360, 420 mg capsules and Parenteral: 5 mg/mL for injection.

Felodipine Oral extended-release: 2.5, 5, 10 mg tablets

Isradipine Oral: 2.5, 5 mg capsules; 5, 10 mg controlled-release tablets

Nicardipine Oral: 20, 30 mg capsules, Oral sustained-release: 30, 45, 60 mg capsules and Parenteral (Cardene I.V.): 2.5 mg/mL for injection.

Nifedipine Oral: 10, 20 mg capsules and Oral extended-release: 30, 60, 90 mg tablets

Nisoldipine Oral: 10, 20, 30, 40 mg extended-release tablets

ADVERSE EFFECTS

- Dizziness or light-headedness

- Peripheral edema & Ankle swelling
- Headache
- Flushing or heat sensation
- Transient hypotension
- Nausea
- Constipation
- Bradycardia
- Rash

DRUG INTERACTION

- Verapamil and diltiazem reduce the elimination and increase the blood levels of carbamazepine (antiepileptics) and simvastatin (hypolipidemics). This can lead to toxicity from these drugs.

- Verapamil and diltiazem raise plasma digoxin levels which may lead to digoxin toxicity.

CONTRAINDICATION

- Patients with preexistent bradycardia, conduction defects, or heart failure caused by systolic dysfunction should not be given CCBs, especially the cardiac selective, non-dihydropyridines CCBs like Verapamil and diltiazem.

- Non-dihydropyridines like Verapamil and diltiazem, should not be administered to patients being treated with a beta-blocker because beta-blockers also depress cardiac electrical and mechanical activity and therefore the addition of a CCB augments the effects of beta-blockade.

Nursing Implication

- Obtain drug history
- Always check blood pressure before starting antihypertensive drug for the first time, if BP is below 90 systolic or 60 beats per minute (BPM) hold the drug and notify doctor.
- Avoidance patient to grapefruit juice during the therapy with CCBs as it may affect metabolism.
- Caution the patient that sudden withdrawal of CCBs may exacerbate angina.

CENTRAL SYMPATHOLYTICS

Drugs used

- **C**lonidine
- **α**-Methyldopa
- **G**uanabenz
- **G**uanfacine

MESSAGE TO STUDENTS: Formula to remember the drug used as central sympatholytics as **"CAGG"**, you can remember as "**C**ountry **A**mong **G**reat **G**iants", which becomes **C**lonidine **α**-Methyldopa**, G**uanabenz and **G**uanfacine. Split the name of the words **C**lo-ni-dine, **α** Methyl-dopa**, G**uan-abenz **and G**uan-facine

MECHANISM OF ACTION

Medulla has α_2 receptors and it plays an important role in increasing sympathetic outflow and thus increases heart rate and blood pressure.

- Centrally acting α2-adrenoceptor agonists (central sympatholytics) acts on α2-adrenoceptor in medulla. This reduces sympathetic outflow to the heart thereby decreasing cardiac output by decreasing heart rate and contractility.

- Reduced sympathetic output to the vasculature decreases sympathetic vascular tone, which causes vasodilation and reduced systemic vascular resistance, which decreases arterial pressure. **(Fig. 10.3.8)**

(Fig. 10.3.8)

USES

Hypertension

DOSE AND ROUTE OF ADMINISTRATION

Clonidine Oral: 0.1, 0.2, 0.3 mg tablets

α-Methyldopa Oral: 250, 500 mg tablets and Parenteral: 50 mg/mL for injection
Guanabenz Oral: 4, 8 mg tablets

Guanfacine(Tenex) Oral: 1, 2 mg tablets

SIDE / ADVERSE EFFECTS

- Sedation, dry mouth and nasal mucosa, bradycardia (because of increased vagal stimulation of the SA node as well as sympathetic withdrawal),
- Orthostatic hypotension and impotence.
- Constipation, nausea and gastric upset are also associated with the sympatholytic effects of these drugs.
- Fluid retention and edema is also a problem with chronic therapy.

DRUG INTERACTION

Anesthestics, other antihypertensives or nitrates + central sympatholytics: Severe fall in BP

Lithium + central sympatholytics: increased risk of lithium toxicity

CONTRAINDICATION

Nursing Implication

- Tell patient that sedation usually occurs when therapy starts and during dosage titration.
- Tell patient not to stop taking drug abruptly.
- Instruct patient to report fever, yellowing of skin or eyes, fatigue, abdominal pain, flulike symptoms, swelling, or significant weight gain.
- Advise patient to move slowly when changing position, to avoid dizziness from sudden blood pressure decrease.
- Report any visible adverse reaction to the doctor.

DIURETICS

- Diuretics are the drugs that help in excretion of large amount of sodium and water through urine thus reducing the sodium and water load in the blood.

- Diuretics lower or antagonize ADH action are diuretic.

We will study normal event that takes place in each segment followed by the drugs acting in each segment

EVENTS THAT TAKES PLACE IN PCT AND DRUGS ACTING ON IT

- Sodium bicarbonate, sodium chloride, glucose, amino acids, and other organic solutes are reabsorbed with the help of specific transport systems in the early part of proximal tubule.
- Reabsorption of sodium bicarbonate and sodium chloride are very important which plays important role in body fluid volume.
- There is no drug acting at this side to inhibit reabsorption of sodium chloride, but there are drugs that can inhibit sodium bicarbonate reabsorption at this site.
- Let us see how sodium bicarbonate is absorbed by normal mechanism.

Before you try to know complete events that takes place in each segment, I will give you an idea about how understand.

First let us divide the event that is taking place under three headings

- **Event in tubular lumen (including luminal membrane)**
- **Event in tubule (including the tubular membrane) and**
- **Event in interstitial blood**

Note: The same pattern will be followed to study the drugs acting on other segments also ok…

A. REABSORPTION OF SODIUM BICARBONATE AT EARLY PART OF PROXIMAL TUBULE (Fig 7.3)

1. Event in tubular lumen (including luminal membrane)

Let us start with luminal urine containing sodium bicarbonate ($NaHCO_3$) which has come from blood ok…

- The sodium (Na^+) from sodium bicarbonate from the tubular lumen gets absorbed in to proximal tubular cell in exchange with hydrogen (H^+) via Na^+/H^+ exchanger.

- Hydrogen (H^+) which is in the tubular lumen now combines with bicarbonate (HCO_3^-) to form carbonic acid (H_2CO_3).

- Carbonic acid (H_2CO_3) is highly unstable and gets split into water (H_2O) and carbondioxide (CO_2) by an enzyme present on luminal membrane called as luminal *Carbonic anhydrase* (CAs).

- Carbondioxide (CO_2) from the lumen diffuses to tubular cell

2. Event in tubular cell (including the tubular membrane)

- The sodium (Na^+) which gets absorbed in to proximal tubule in exchange with hydrogen (H^+) via Na^+/H^+ exchanger will be go to interstitial blood in exchange with potassium (K^+) via Na^+ / K^+ ATP ase.

- Carbondioxide (CO_2) from the lumen that diffuses to tubular cell gets combined to cellular water (H_2O) to form carbonic acid (H_2CO_3).

- Here also the formed cellular carbonic acid (H_2CO_3) is unstable and gets split to hydrohen (H^+) and bicarbonate (HCO_3^-) by an enzyme present towards cell called as cellular *Carbonic anhydrase* (CAs).

- Hydrogen (H^+) gets to tubular lumen in exchange with sodium (Na^+) via Na^+/H^+ exchanger

- Bicarbonate (HCO_3^-) from the tubular cell goes to interstitial blood via transporter.

3. Event that takes place in interstitial blood

Sodium (Na^+) and bicarbonate (HCO_3^-) which is in the interstitial blood gets combined to form sodium bicarbonate ($NaHCO_3$)

Please recall that we have started with sodium bicarbonate ($NaHCO_3$) in the luminal urine and ended with sodium bicarbonate ($NaHCO_3$) in the interstitial blood. This is how the sodium bicarbonate ($NaHCO_3$) gets absorbed from urine to blood.

DRUGS ACTING ON EARLY PART OF PROXIMAL TUBULE

CARBONIC ANHYDRASE (CAs) INHIBITORS

DRUGS USED

- **A**cetazolamide
- **B**rinzolamide
- **D**orszolamide

MESSAGE TO STUDENT: Formula to remember *Carbonic anhydrase* (CAs) inhibitors is **"ABD",** you can remember as "**After Birth Day",** which becomes **A**cetozolamide, **B**rinzolamide and **D**orzolamide. Here the last word of all the drugs ends with **"Zolamide"** and you have to remember **Aceta, Brin and Dor,** which finally becomes **Aceto-**zolamide, **Brin-**zolamide **and Dor-**zolamide.

MECHASNISM OF ACTION

- Now our aim is to prevent sodium bicarbonate absorption. Fortunately we have a drug that act at this site called as *Carbonic anhydrase* (CAs) inhibitors

- *Carbonic anhydrase* (CAs) inhibitors inhibit enzyme luminal *Carbonic anhydrase* (CAs) and hence prevent bicarbonate reabsorption (**Fig 7.4)**

(**Fig 7.4)**

USES

As more and more bicarbonate which is not absorbed and remains in the urine, it may increase luminal pH and decrease blood pH leading to metabolic acidosis which is very dangerous, hence *Carbonic anhydrase* (CAs) inhibitors even though has diuretic property but usually are not used for diuretic purposes.

OTHER USES

- **Urinary Alkalinization:** As it inhibits bicarbonate reabsorption and increase luminal pH, *Carbonic anhydrase* (CAs) inhibitors are used as Urinary Alkalinizer.

This is very useful to remove any poisonous acidic drugs which may get absorbed if urine is also acidic. But alkalinization of urine makes acidic drugs to get ionized and hence its excretion increases in urine.

- **Glaucoma:** It is a condition where there is increased intra ocular pressure due to excess aqueous humour production or decreased drainage. For the production of aqueous humour sodium bicarbonate is needed and it gets secreted in the same way as it occurs in renal tubule.

Carbonic anhydrase (CAs) inhibitor inhibits *Carbonic anhydrase* enzyme and decrease the production of aqueous humour.

- **Acute Mountain Sickness:**

Formation of cerebrospinal fluid (CSF) needs sodium bicarbonate which has the same mechanism as we saw in the renal tubule. When a person climbs suddenly to a high altitude, the formation of CSF increases and pH of CSF also increases. This leads to acute mountain sickness with symptoms like Weakness, dizziness, insomnia, headache, and nausea.

Carbonic anhydrase (CAs) inhibitors inhibit *Carbonic anhydrase* and decrease the production of formation of CSF and decrease pH of CSF.

- **Metabolic Alkalosis**

Metabolic alkalosis is an increase in blood pH which can be dangerous in patient with heart disease and decrease in blood pH can be life saving.

Carbonic anhydrase (CAs) inhibitors prevents reabsorption of sodium bicarbonate and decrease blood pH, thus can be very useful in metabolic alkalosis.

DOSE AND ROUTE OF ADMINISTRATION

Acetazolamide

Oral: 125, 250 mg tablets

Oral sustained-release: 500 mg capsules

Brinzolamide

Ophthalmic: 1% suspension

Dorzolamide

Ophthalmic: 2% solution

ADVERSE EFFECTS

Hyperchloremic Metabolic Acidosis

Renal Stones

DRUG INTERACTION

Acetazolamide + potassium-sparing diuretics: increased metabolic acidosis and hyperkalemia

Acetazolamide + Quinidine: Acetazolamide decreases excretion of Quinidine by increasing urinary pH.

CONTRAINDICATIONS

Liver cirrhosis

Nursing Implication

- Assess for allergy and contraindications: allergy to sulfa, severe renal or hepatic disease
- Monitor for adverse drug reaction and inform doctor if any.
- Assess daily weight, fluis Input & urine Output , serum

B. REABSORPTION OF WATER FROM LATE PCT AND DESCENDING LIMB OF HENLE'S LOOP

- Late part of the PCT and descending limb of henle's loop is highly permeable to water and large amount of water can get absorbed from this segment.

- So any drug that prevent water absorption from this segment will lead to excess of water loss in urine as no other portion of the nephron is permeable. (**Fig 7.5)**
- So any drug that prevents the water reabsorption at this segment due to osmotic effect can be a good diuretic.

(Fig 7.5)

DRUGS ACTING ON PCT AND DESCENDING LIMB OF HENLE'S LOOP

OSMOTIC DIURETICS

DRUGS USED

Mannitol

MESSAGE TO STUDENT: Formula to remember the drug under osmotic diuretics is **"O",** are you confused? Here **"O"** means osmotic diuretics and mannitol also has the word **"O".** You split the word and remember as **"Man-ni-tOl"**

MECHASNISM OF ACTION

- It is an impermeant solute which is only filtered, but neither secreted nor reabsorbed.
- Once inside the tubular lumen, then it even if water tries to get absorbed then the concentration of the solute increases and prevents further water reabsotption due to osmotic effect.
- Once the water does not get absorbed at this segment due to effect of osmotic diuretic, it cannot get absorbed in other segment as well also as they are not permeable to water. Hence osmotic diuretics lead to excretion of more water than other solutes. This is called as water dieresis. (**Fig 7.6)**

(Fig 7.6)

USES

Anuria or oliguria: It is a condition where urine is not formed properly or its volume is reduced. Mannitol is useful in these conditions

Reduction of Intracranial and Intraocular Pressure: In these the intracellular fluid increases which may lead to complication. Mannitol reduces intracranial and intraocular pressure.

DOSE AND ROUTE OF ADMINISTRATION

Parenteral: 5, 10, 15, 20, 25% for i.v injection

To decrease intracranial pressure: A dose of 1–2 g/kg mannitol is administered intravenously.

ADVERSE EFFECTS

Extracellular Volume Expansion: Due to extraction of water from the cell leads to Headache, nausea, and vomiting

Dehydration and Hypernatremia: Due to extreme water loss in urine and increased sodium in blood

DRUG INTERACTION

Mannitol + Lithium (antimanic): Increased urinary excretion of lithium

CONTRAINDICATIONS

- In heart failure and pulmonary congestion, it may cause pulmonary oedema.
- Liver dysfunction, Oliguria due to renal disease and patient suffering from intracranial bleeding.

NURSING IMPLICATION

- Some oliguric patients do not respond to an osmotic diuretic. Therefore, a test dose of mannitol (12.5 g intravenously) should be given prior to starting a continuous infusion.
- Mannitol should not be continued unless there is an increase in urine flow rate to more than 50 mL/h during the 3 hours following the test dose.
- Mannitol (12.5–25 g) can be repeated every 1–2 hours to maintain urine flow rate greater than 100 mL/h.
- Prolonged use of mannitol is not advised.

C. REABSORPTION OF SODIUM CHLORIDE (Nacl) FROM THICK ASCENDING LIMB (Fig 7.7)

1. Event in tubular lumen (including luminal membrane)

- Sodium chloride (NaCl) present in the luminal urine reaches lumen of thick ascending limb.
- A symporter called Sodium-Potassium-2 Chloride ($Na^+/K^+/2Cl^-$) present on the luminal membrane operates and helps in the absorption of Sodium, Potassium and Chloride in to tubular cell.

2. Event in tubular cell (including the tubular membrane)

- The sodium (Na^+) which gets absorbed in to tubular cell will be go to interstitial blood in exchange with potassium (K^+) that comes to tubular cell from interstitial blood via Na^+ / K^+ ATP ase .

- The chloride (Cl^-) also enters interstitial blood from tubular cell by the help of other transporter.

3. Event that takes place in interstitial blood

- The sodium (Na^+) and chloride (Cl^-) combines in interstitial blood to form NaCl.

- Please recall that we have started with sodium chloride (NaCl) in the luminal urine of thick ascending limb and ended with sodium chloride (NaCl) in the interstitial blood. This is how the sodium chloride (NaCl) gets absorbed from urine to blood. About 35-40% of sodium gets absorbed at this segment.

(Fig 7.7)

Note:

The potassium (K+) that has entered the tubular cell from the lumen of thick ascending limb due to action of $Na^+/K^+/2Cl^-$ and the potassium (K+) that has entered from interstitial blood to tubular cell will increase intracellular potassium (K+) level.

So, the increased intracellular potassium (K+) will back diffuse to tubular lumen of thick ascending limb, thus the luminal potassium (K+) level increase.

Increased luminal potassium (K+) level will favors for re-absorption of calcium ($Ca2^+$) and Magnesium (Mg2+) from tubular lumen to interstitial blood via paracellular pathway.

DRUGS ACTING ON THICK ASCENDING LIMB

LOOP DIURETICS / HIGH EFFICACY OR HIGH CEILING DIURETICS

DRUGS USED

Furosemide

Torsemide

MESSAGE TO STUDENTS : Formula to drugs under loop diuretics is **"FT",** you can remember as "Fine Touch", which becomes **F**urosemide and **T**orsemide. Here the names of both

the drugs ends with common word “semide”, you have to remember “Furo and Tor”, which becomes **F**uro-semide and **T**or-semide

MECHANISM OF ACTION

Loop diuretics inhibit $Na^{+}/K^{+}/2Cl^{-}$ symporter and mainly prevent the absorption of Sodium ($Na^{+)}$ and chloride (Cl^{-}) along with inhibition of absorption of K^{+}.

Maximum absorption of sodium can be prevented by inhibiting $Na^{+}/K^{+}/2Cl^{-}$ symporter. (**Fig 7.8)**

(Fig 7.8)

USES

- Hypertesion
- Hyperkalemia
- Heart failure
- Acute pulmonary edema and other edematous conditions
- Acute renal failure
- Acute hypercalcemia
- Anion disease

MESSAGE TO STUDENTS : Formula to remember uses of loop diuretics are 3H and 3A, which becomes **H**ypertesion, **H**yperkalemia, **H**eart failure, and **A**cute pulmonary edema and other edematous conditions, **A**cute renal failure and **A**cute hypercalcemia

DOSE AND ROUTE OF ADMINISTRATION

Oral Furosemide 20–80 mg (Furosemide i.v is also available (8 mg/mL solutions))

Oral Torsemide 2.5–20 mg

ADVERSE EFFECTS

- Allergic Reactions
- Hypokalemia (decreased serum K^{+} level)
- Hypomagnesemia (decreased serum Mg^{+} level)
- Hypocalcaemia (decreased serum Ca^{2+} level)

Note: You may think why Hypokalemia (decreased serum K^+ level), Hypomagnesemia (decreased serum Mg^+ level) and Hypocalcaemia (decreased serum Ca^{2+} level) occurs when loop diuretics are given.

Reason for Hypomagnesemia (decreased serum Mg^+ level) and Hypocalcaemia (decreased serum Ca^{2+} level)

- Please recall that he potassium (K+) that has entered the tubular cell from the lumen of thick ascending limb due to action of $Na^+/K^+/2Cl^-$ and the potassium (K+) that has entered from interstitial blood to tubular cell will increase intracellular potassium (K+) level.

- So, the increased intracellular potassium (K+) will back diffuse to tubular lumen of thick ascending limb, thus the luminal potassium (K+) level increase.

- Increased luminal potassium (K+) level will favors for re-absorption of calcium ($Ca2^+$) and Magnesium (Mg2+) from tubular lumen to interstitial blood via paracellular pathway.

- So if you inhibit $Na^+/K^+/2Cl^-$ symporter then intracellular potassium will not increase and hence potassium will not back diffuse and there will be no luminal positive potential, hence Mg^+ and Ca^{2+} does not get absorbed leading to hypomagnesaemia (decreased serum Mg^+ level) and Hypocalcaemia (decreased serum Ca^{2+} level)

Reason for Hypokalaemia (decreased serum K^+ level)

- When absorption of sodium prevented in thick ascending limb by inhibiting $Na+/K+/2Cl^-$ symporter, more sodium reaches collecting duct where sodium gets absorbed via sodium channel with secretion of potassium in to collecting duct which gets finally excreted in urine, thus leading to hypokalaemia.

- Hence loop diuretics are combined with potassium sparing diuretics to prevent potassium loss.

DRUG INTERACTION

NSAIDs + Loop diuretics: Efficacy of loop diuretic gets reduced

Bile acid-binding resins + Loop diuretics: Decreased absorption of Loop diuretics

CONTRAINDICATION

History of allergy to the drug

In Hepatic cirrhosis or renal failure, or heart failure

NURSING IMPLICATION

- Obtain history of drug allergy
- Monitor the condition of the patient for the response
- Check the lab report and correlate with clinical response
- Check for the signs of dehydration
- Furosemide i.v should be given slowly, not faster than 20 mg/min
- Evaluate signs of ototoxicity
- Don't administer furosemide concurrently with aminoglycoside (e.g. gentamicin) which also is ototoxic

D. REABSORPTION OF SODIUM CHLORIDE (NaCl) FROM DISTAL CONVOLUTED TUBULE . (**Fig 7.9)**

1. Event in tubular lumen (including luminal membrane)

NaCl in the luminal urine present in the **distal convoluted tubule** is reabsorbed via sodium chloride symporter present on the luminal membrane.

2. Event in tubular cell (including the tubular membrane)

The sodium (Na^+) which gets absorbed in to tubular cell will be go to interstitial blood in exchange with potassium (K^+) that comes to tubular cell from interstitial blood via Na^+ / K^+ ATP ase .

The chloride (Cl^-) also enters interstitial blood from tubular cell by the help of other transporter.

3. Event that takes place in interstitial blood

The sodium (Na^+) and chloride (Cl^-) combines in interstitial blood to form NaCl.

. (**Fig 7.19)**

DRUGS ACTING ON DISTAL CONVOLUTED TUBULE

THIAZIDES DIURETICS

DRUGS USED

Hydrochlorothiazide

Hydroflumethiazide

MESSAGE TO STUDENT: Formula to remember the drug under thiazides is **"HH",** The starting name and ending name of both the drugs are **"Hydro"** and **"thiazide".** You have to remember the middle word as **"chloro"** and **"flume",** which becomes **Hydro-chloro-thiazide** and **Hydro-flume-thiazide**

MECHANISM OF ACTION

Thiazide diuretics inhibit Na^{+}/Cl^{-} symporter and mainly prevent the absorption of Sodium ($Na^{+)}$ and chloride (Cl^{-}). (**Fig 7.10)**

(**Fig 7.10)**

USES

- Hypertension
- Diabetes Insipidus
- Nephrolithiasis (due to calcium)

DOSE AND ROUTE OF ADMINISTRATION

Hydrochlorothiazide 25–100 mg As single dose

Hydroflumethiazide 25–100 mg In two divided doses

ADVERSE EFFECTS

Allergic Reactions

Hypokalemia (decreased serum K^{+} level)

Hyperglycemia

Hyperlipidemia

Reason for Hypokalaemia (decreased serum K^{+} level)

- When absorption of sodium is prevented in thick ascending limb by inhibiting $Na+/K+/2Cl^{-}$ symporter, more sodium reaches collecting duct where sodium gets absorbed via sodium channel with secretion of potassium in to collecting duct which gets finally excreted in urine, thus leading to hypokalaemia.

- Hence thiazides diuretics are also are combined with potassium sparing diuretics to prevent potassium loss.

DRUG INTERACTION

CONTRAINDICATION

NURSING IMPLICATION

- Obtain history of drug allergy
- Monitor the condition of the patient for the response
- Check the lab report and correlate with clinical response
- Check for the signs of dehydration

D. REABSORPTION OF SODIUM (Na^+) AND SECRETION OF POTASSIUM (K^+) FROM COLLECTING DUCT

- We already know that when absorption of sodium is prevented in thick ascending limb by inhibiting Na+/K+/$2Cl^-$ symporter or by inhibiting Na+/ Cl^- symporter in distal convolute tubule, then more sodium reaches collecting duct where sodium gets absorbed via sodium channel with secretion of potassium in to collecting duct which gets finally excreted in urine, thus leading to hypokalaemia.

- When more sodium reaches collecting duct, Aldosterone (mineralocorticoid) diffuses in to tubular cell from interstitial blood and binds to aldosterone receptors in the tubular cell.

- Aldosterone and aldosterone receptor forms a complex and translocates to nucleus and binds to specific element of DNA. (**Fig 7.11)**

(Fig 7.11)

- DNA synthesis mRNA which directs ribosomes to synthesis a protein called Aldosterone induced protein (AIP).

- Aldosterone induced protein (AIP) will stimulate sodium channel in the collecting duct and causes sodium absorption in exchange with potassium secretion in to collectinh duct from tubular cell.

- Thus more the sodium reaches the collecting duct, more the sodium absorption from collecting duct and more the potassium secretion into luminal urine which gets excreted leading to hypokalaemia.

DRUGS ACTING ON COLLECTING DUCT

POTASSIUM (K^+) SPARING DIURETICS

ALDOSTERONE ANTAGONIST: Spironolactone

SODIUM CHANNEL BLOCKERS: Amiloride and **T**riampterene

ALDOSTERONE ANTAGONIST

DRUGS USED

Spironolactone

MECHANISM OF ACTION

Spironolactone antagonizes aldasterone and hence inhibits sodium absorption (Na^+) and potassium (K^+) secretion. (**Fig 7.12)**

(**Fig 7.12)**

USES

Given along with furosemide or thiazide in hypertension to prevent hypokalaemia induced by furosemide or thiazide

Hyperaldosteronism condition like Conn's syndrome, ectopic ACTH production) or to secondary aldosteronism (from heart failure, hepatic cirrhosis, nephrotic syndrome)

DOSE AND ROUTE OF ADMINISTRATION

Oral: 25, 50, 100 mg tablets

Dose : 50–100 mg/day

ADVERSE EFFECTS

- Hyperkalemia
- Hyperchloremic Metabolic Acidosis
- Gynecomastia
- Acute Renal Failure
- Kidney Stones

DRUG INTERACTION

ACE inhibitors

Concomitant administration of ACE inhibitors with potassium-sparing diuretics has been associated with severe hyperkalemia.

Alcohol, barbiturates, or narcotics

Potentiation of orthostatic hypotension may occur.

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalemia, may occur. Alcohol, Milk product containing potassium and high salt diet

CONTRAINDICATION

Contraindicated for patients with anuria, acute renal insufficiency, significant impairment of renal excretory function, or hyperkalemia.

Nursing Implication

- Check blood pressure before initiation of therapy and at regular intervals throughout therapy.
- Lab tests: Monitor serum electrolytes (sodium and potassium) especially during early therapy; monitor digoxin level when used concurrently.
- Assess for signs of fluid and electrolyte imbalance, and signs of digoxin toxicity.
- Monitor daily Input & Output and check for edema. Report lack of diuretic response or development of edema; both may indicate tolerance to drug.
- Weigh patient under standard conditions before therapy begins and daily throughout therapy. Weight is a useful index of need for dosage adjustment. For patients with ascites, physician may want measurements of abdominal girth.
- Observe for and report immediately the onset of mental changes, lethargy, or stupor in patients with liver disease.
- Adverse reactions are generally reversible with discontinuation of drug. Gynecomastia appears to be related to dosage level and duration of therapy; it may persist in some after drug is stopped.
- Be aware that the maximal diuretic effect may not occur until third day of therapy and that diuresis may continue for 2–3 d after drug is withdrawn.
- Report signs of hyponatremia or hyperkalemia, most likely to occur in patients with severe cirrhosis.
- Avoid replacing fluid losses with large amounts of free water (can result in dilutional hyponatremia).
- Weigh 2–3 times each week. Report gains/loss of 5 lb.
- Advice patient to avoid excessive intake of high-potassium foods and salt substitutes.
- Advice patient not to breast feed while taking this drug.

SODIUM CHANNEL BLOCKERS

DRUGS USED

- **A**miloride
- **T**riampterene

MESSAGE TO STUDENT: Formula to remember sodium channel blockers is **"AT",** you can remember as **"After Travel"**, which becomes **Amiloride** and **Triampterene.** You can split the words and remember as **Ami-lo-ride** and **Tri-amp-te-rene**

MECHANISM OF ACTION

We already know that aldosterone action will result in Na^+ re-absorption via sodium channel and increases K^+ secretion via potassium channel.

Sodium channel blockers will block sodium channel in collect duct and prevents Na^+ re-absorption which also prevents potassium secretion in to luminal urine in collecting dust. This will prevent hypokalaemia. **Fig 7.13**

Fig 7.13

USES

- Given along with furosemide or thiazide in hypertension to prevent hypokalaemia induced by furosemide or thiazide.
- Primary hyperaldosteronism.
- In hypokalaemia.

DOSE AND ROUTE OF ADMINISTRATION

Oral Amiloride 5 mg Once daily

Oral Triamterene 50 mg 1–3 times daily

ADVERSE EFFECTS

Headache, dizziness, nausea, vomiting, loss of appetite, abdominal pain or diarrhea may occur.

DRUG INTERACTION

ACE inhibitors or potassium supplement + Sodium channel blockers like amiloride and triampterene : Increases serum potassium level leading to hyperkalaemia

CONTRAINDICATION

- Elevated serum potassium (>5.5 mEq/L)
- Concomitant use of other potassium-sparing diuretics
- In anuria, acute or chronic renal insufficiency; evidence of diabetic nephropathy; or type 1 diabetes mellitus, metabolic or respiratory acidosis and hepatic function impairment.

NURSING IMPLICATION

- Monitor for Signs & Symptoms of hyperkalemia and hyponatremia .
- Lab tests: Serum potassium levels should be monitered, particularly when therapy is initiated, whenever dosage adjustments are made, and during any illness that may affect kidney function.
- Intermittent evaluations of Blood Urea Nitrogen , creatinine, and ECG for patients with renal or hepatic dysfunction, diabetes mellitus, older adults, or the debilitated should be done.

VASODILATORS

Vasodilator drugs can be divided into

- **Selective arteriolar dilators : H**ydralazine, **M**inoxidil, **D**iazoxide and **F**enoldopam
- **Venous dilators: N**itrates
- **Arterial and venous dilators : S**odium nitroprusside

SELECTIVE ARTERIOLAR DILATORS

DRUGS USED

- **H**ydralazine
- **M**inoxidil
- **D**iazoxide
- **F**enoldopam

MESSAGE TO STUDENTS: Formula to remember the drug used as selective arteriolar dilators is **"HMDF",** you can remember as **"H**ead **M**aster **D**istant **F**riend**".** which becomes **H**ydralazine, **M**inoxidil, **D**iazoxide and **F**enoldopam. Remember the names of the drugs by splitting the words as **H**ydra-la-zine, **M**in-oxi-dil, **D**ia-zo-xide and **F**en-oldo-pam

MECHANISM OF ACTION

- **H**ydralazine, **M**inoxidil and **D**iazoxiden opens potassium channels in arteolar smooth muscle and stabilizing the membrane potential at the resting level, thus leads to arteolar dilatation.

- **F**enoldopam acts primarily as an agonist of dopamine D_1 receptors in arteolar smooth muscle resulting in dilation of peripheral arteries and natriuresis (increased excretion of sodium).
- Dilatation of peripheral arteries leads to decreased afterload and reduce cardiac workload. **(Fig 10.3.9)**

(Fig 10.3.9)

USES

Congestive heart failure

DOSE AND ROUTE OF ADMINISTRATION

Hydralazine Oral: 10, 25, 50, 100 mg tablets

Minoxidil Oral: 2.5, 10 mg tablets

Diazoxide Oral (Proglycem): 50 mg capsule; 50 mg/mL oral suspension and Parenteral: 15 mg/mL ampule

Fenoldopam Parenteral: 10 mg/mL for IV infusion

ADVERSE EFFECTS

- **H**ydralazine: Headache, nausea, anorexia, palpitations, sweating, and flushing.
- Minoxidil: Headache, sweating, and hirsutis
- Diazoxide: Hypotension
- Fenoldopam: Tachycardia, headache, and flushing

DRUG INTERACTION

- **H**ydralazine + Nonsteroidal anti-inflammatory drugs: Decreased antihypertensive response to hydralazine.
- **M**inoxidil + Calcium channel blockers or central sympatholytics: increased fluid retention
- **D**iazoxide: Since diazoxide is highly bound to serum proteins, it may displace other substances which are also bound to protein, such as bilirubin or coumarin (warfarin- oral anticoagulant) and its derivatives, resulting in higher blood levels of these substances.
- **F**enoldopam iv increases effects of carvedilol oral by added drug effects

CONTRAINDICATION

- Coronary artery disease
- Aortic stenosis
- Mitral stenosis

Nursing Implication

- Advice patient not to discontinue the drug abruptly
- Drug tolerance may develop so keep checking for the drug response
- As these may cause orthostatic hypotension – advice patient to change position slowly
- Inform patients that palpitations may occur during early stages of therapy.
- Monitor the weight of the patient daily.

VENOUS DILATORS

DRUG USED

Nitrates : Isosorbide dinitrate

MECHANISM OF ACTION

- Isosorbide dinitrate is denitrated by *glutathione S-transferase*.
- Free nitrite ion is released, which is then converted to nitric oxide causes activation of *guanylyl cyclase* and an increase in cGMP
- Increased cGMP, dephosphorylate *myosin light chain kinase* (MLCK) which interrupt the interaction of actin-myosin in vascular smooth muscle (especially in veins)
- Dilatation of veins leads to decreased preload and reduce cardiac workload. **(Fig 10.3.10)**

(Fig 10.3.10)

USES

Congestive heart failure

DOSE AND ROUTE OF ADMINISTRATION

Isosorbide dinitrate, oral 10–60 mg per 4–6 hours

ADVERSE EFFECTS

- Orthostatic Hypotension
- Tachycardia
- Throbbing Headache

DRUG INTERACTION

- Increased hypotensive effects with alcohol or vasodilators. Marked orthostatic hypotension may occur when used with calcium channel blockers.
- Vasodilatory effect may be reduced with dihydroergotamine.

CONTRAINDICATION

In case of intracranial pressure

- Obstructive Hypertrophic Cardiomyopathy
- Severe Fluid Deficiency
- Inferior Myocardial Infarction With Right Ventricular Involvement
- Raised Intracranial Pressure
- Cardiac Tamponade.

Nursing Implication

- **History:** Allergy to nitrates, severe anemia, GI hypermobility, head trauma, cerebral hemorrhage, hypertrophic cardiomyopathy, pregnancy, lactation

- **Physical:** Skin color, temperature, lesions; orientation, reflexes, affect; orthostatic BP, baseline ECG, peripheral perfusion, adventitious sounds, liver evaluation, normal output.

- Give oral preparations on an empty stomach, 1 hr before or 2 hr after meals; take with meals if severe, uncontrolled headache occurs.

- Keep life support equipment readily available if overdose occurs or cardiac condition worsens.

- You may experience these side effects: Dizziness, light-headedness (may be transient; use care to change positions slowly) and headache

- Report blurred vision, persistent or severe headache and rash.

ARTERIAL AND VENOUS DILATORS

DRUG USED

Sodium nitroprusside

MECHANISM OF ACTION (Fig 10.3.11)

- Sodium nitroprusside cause activation of guanylyl cyclase, either via release of nitric oxide or by direct stimulation of the enzymein the vascular smooth muscle in both arteries and veins.
- The result is increased intracellular cGMP, which relaxes vascular smooth muscle, thus venodilatation leads to decreased preload and arteriolar dilatation leads to decreased afterload

(Fig 10.3.11)

USES

Congestive heart failure

DOSE AND ROUTE OF ADMINISTRATION

Dose is i.v infusion at 0.5 g/kg/min and may be increased up to 10 g/kg/min.

ADVERSE EFFECTS

- Metabolic acidosis, arrhythmias, excessive hypotension.

- Accumulation of cyanide may lead to cyanide poisoning (as nitroprusside is a complex of iron, cyanide groups, and a nitroso moiety)

Treatment

- Administration of sodium thiosulfate as a sulfur donor facilitates metabolism of cyanide.

- Hydroxocobalamin combines with cyanide to form the nontoxic cyanocobalamin.

- Both have been advocated for prophylaxis or treatment of cyanide poisoning during nitroprusside infusion.

DRUG INTERACTION

Increased systolic BP and decreased antihypertesive effect if taken concurrently with ergot alkaloids.

CONTRAINDICATION

Contraindicated with allergy to nitrates, severe anemia, head trauma, cerebral hemorrhage, hypertrophic cardiomyopathy, narrow-angle glaucoma and postural hypotension.

Nursing Implication

- Monitor constantly to titrate (either increase or decrease the dose) IV infusion rate to BP response.
- Relieve adverse effects by slowing IV rate or by stopping drug; minimize them by keeping patient supine.
- Notify physician immediately if BP begins to rise after drug infusion rate is decreased or infusion is discontinued.

- Monitor fluid Input & urine output

- Lab tests: Monitor blood thiocyanate level in patients receiving prolonged treatment or in patients with severe kidney dysfunction (levels usually are not allowed to exceed 10 mg/dL). Determine plasma cyanogen level following 1 or 2 d of therapy in patients with impaired liver function.

CHAPTER 10.4

ANTI-ANGINALS

Angina= A kind of feeling of suffocation or tightness

Pectoris= In the region of pectoral or chest region

Angina pectoris is the severe chest pain starting from left side of the chest and radiating towards inner aspect of arm, forearm upto middle, ring and little finger due to inadequate coronary blood flow and reduced supply of oxygen to a part of myocardium. **(Fig 10.4.1)**

(Fig 10.4.1)

TYPES OF ANGINA

1. **Classic angina / atherosclerotic angina:**

Cause: Atheromatous obstruction of the large coronary vessels leads to imbalance between the oxygen requirement of the heart and the oxygen supplied to it via the coronary vessels. **(Fig 10.4.2)**

(Fig 10.4.2)

Symptoms: Pain occurs during exertion after heavy exercise or any other hard work

2. **Unstable angina: (Fig 10.4.3)**

Cause: Increased epicardial coronary artery smooth muscle tone or small platelet clots occurring in the vicinity of an atherosclerotic plaque.

(Fig 10.4.3)

Symptoms: Pain can occur even at rest

3. **Variant angina or Prinzmetal's angina or vasospastic or angiospastic angina: (Fig 10.4.4)**

Cause: Localized portions of coronary blood vessels associated with atheromas leading to myocardial ischemia and pain

(Fig 10.4.4)

Symptoms: Pain can occur either during exertion or at rest.

Treatment strategy

- Decreasing oxygen demand by myocardium
- Increasing delivery of O_2 (by increasing coronary flow) to myocardium

CLASSIFICATION OF ANTI-ANGINAL DRUGS

I. Drugs to get immediate relief from angina

Nitrates (vasodilators)

Short acting:

- Nitroglycerin
- Isosorbide dinitrate
- Amyl nitrite

Long acting:

- Nitroglycerin
- Isosorbide dinitrate (sublingual)
- Isosorbide mononitrate

II. Prophylactic Drugs used in angina

a) Calcium channel blockers (vasodilators)

Non-dihydropyridines

- **Phenylalkylamine : V**erapamil
- **Benzothiazepine : D**iltiazem

Dihydropyridine

- **F**elodipine
- **I**sradipine
- **A**mlodipine
- **N**icardipine
- **N**ifedipine
- **N**isoldipine

b) β blockers

- Metoprolol
- Atenolol
- Bisoprolol

} Selective β_1 blocker

III. Potassium channel openers

Nicorandil

IV Other drugs

Hypolipidemics, Antiplatelets, Antioxidants etc

NITRATES

Short acting:

- Nitroglycerin
- Isosorbide dinitrate
- Amyl nitrite

Long acting:

- Nitroglycerin
- Isosorbide dinitrate (sublingual)
- Isosorbide mononitrate

MESSAGE TO STUDENTS: Formula to remember nitrates is **"NIA"** for short acting and **"NII"** for long acting. Nitroglycerine and isosorbide dinitrate is common for both short and long acting nitrates. Remember Amyl-nitrate as third drug in short acting and isosorbide mononitrate for long acting.

MECHANISM OF ACTION (Fig 10.4.5)

- Nitrates get denitrated by glutathione *S*-transferase.
- Free nitrite ion is released, which is then converted to nitric oxide (NO) causes activation of guanylyl cyclase and an increase in cGMP
- Increased cGMP, dephosphorylate myosin light chasin kinase which interrupt the interaction of actin-myosin in vascular smooth muscle (especially in veins)

- Dilatation of veins leads to decreased preload and reduce cardiac workload and myocardial O_2 demand.
- In some patients, a redistribution of coronary flow may increase oxygen delivery to ischemic tissue.
- In variant angina, the nitrates and the calcium channel blockers may also increase myocardial oxygen delivery by reversing coronary arterial spasm.

(Fig 10.4.5)

Other Smooth Muscle Organs

Relaxation of smooth muscle of the bronchi, gastrointestinal tract (including biliary system), and genitourinary tract.

Action on Platelets

Decreases platelet aggregation

USES

Classic angina / atherosclerotic angina
Unstable angina
Variant angina or Prinzmetal's angina or vasospastic or angiospastic angina

Sublingual nitroglycerin

Nitrates has rapid onset of action (1–3 minutes), sublingual route of nitroglycerin administration is the most frequently used agent for acute attack of angina.

Advantage:

- Has rapid onset of action
- Gets absorbed thorough sublingual vein, hence bypasses liver
- After getting relief from pain, the remaining tab can be spitted out.

Disadvantage

Because its duration of action is short (not exceeding 20–30 minutes), it is not suitable for maintenance therapy.

Other uses

Congestive heart failure

- Dilatation of veins leads to decreased preload and reduce cardiac workload and myocardial O_2 demand.

Myocardial infarction

- Slow i.v infusion relieves pulmonary congestion and dilatation of veins leads to decreased preload and reduce cardiac workload and myocardial O_2 demand

Cyanide poisoning

- Cyanide reacts and inhibits cytochrome and other oxidative enzyme which results in tissue hypoxia.
- Nitrite ion reacts with hemoglobin (which contains ferrous iron) to produce methemoglobin (which contains ferric iron).
- Methemoglobin has high affinity to cyanide and regenerate active other oxidative enzyme **(Fig 10.4.6 & 10.4.7)**

Cytochrome + Cyanide
and other
Oxidative enzyme

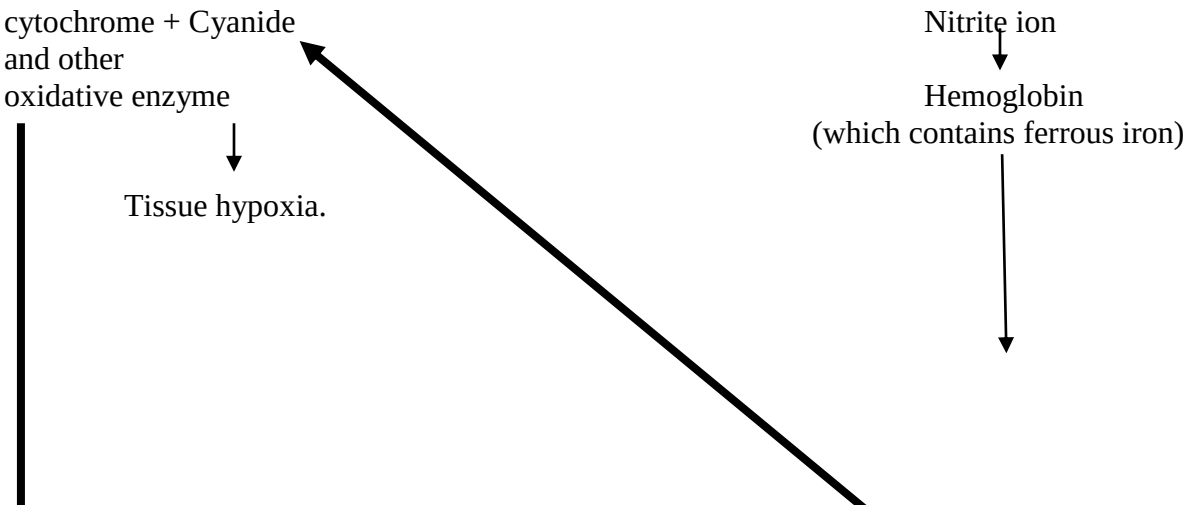
↓

Inhibition of Cyanide
and other
Oxidative enzyme

↓

Tissue hypoxia.
(Fig 10.4.6)

Action of nitrates



Methemoglobin
(contains ferric iron).

Regeneration of cytochrome and other oxidative enzyme

↓

Normal cellular function

(Fig 10.4.7)

DOSE AND ROUTE OF ADMINISTRATION

Isosorbide dinitrate, oral 10–60 mg per 4–6 hours

ADVERSE EFFECTS

- Orthostatic Hypotension
- Tachycardia
- Throbbing Headache

DRUG INTERACTION

- Increased hypotensive effects with alcohol or vasodilators. Marked orthostatic hypotension may occur when used with calcium channel blockers.

- Vasodilatory effect may be reduced with dihydroergotamine.

CONTRAINDICATION

In case of intracranial pressure

- Obstructive Hypertrophic Cardiomyopathy
- Severe Fluid Deficiency
- Inferior Myocardial Infarction With Right Ventricular Involvement
- Raised Intracranial Pressure
- Cardiac Tamponade.

Nursing Implication

- **History:** Allergy to nitrates, severe anemia, GI hypermobility, head trauma, cerebral hemorrhage, hypertrophic cardiomyopathy, pregnancy, lactation

- **Physical:** Skin color, temperature, lesions; orientation, reflexes, affect; orthostatic BP, baseline ECG, peripheral perfusion, adventitious sounds, liver evaluation, normal output.

- Give oral preparations on an empty stomach, 1 hr before or 2 hr after meals; take with meals if severe, uncontrolled headache occurs.

- Keep life support equipment readily available if overdose occurs or cardiac condition worsens.

- You may experience these side effects: Dizziness, light-headedness (may be transient; use care to change positions slowly) and headache

- Report blurred vision, persistent or severe headache and rash.

CALCIUM CHANNEL BLOCKERS

DRUGS USED

Non-dihydropyridines

- **Phenylalkylamine : V**erapamil

- **Benzothiazepine : D**iltiazem

Dihydropyridine

- **F**elodipine
- **I**sradipine
- **A**mlodipine
- **N**icardipine
- **N**ifedipine
- **N**isoldipine

MESSAGE TO STUDENTS: Formula to remember the drug used as calcium channel blockers is **V.D. FIAN[3],** you can remember as **"V**ictory **D**ay **F**or **I**ndia **A**fter **N**oble[3]**".** Under **Phenylalkylamines** remember the drug **"V"** by splitting the word as "**Vera-pa-mil"** and under **benzothiazepine,** remember the drug **"D"** by splitting the word as **"Dil-tia-zem".**

Under **Dihydropyridine** , the names of all the drugs ends with a common word **"dipine",** you have to remember **F**elo, **I**sra**, A**mlo**, N**icar**, N**ife and **N**isol, which becomes **Felo**-dipine**, Isra**-dipine**, Amlo**-dipine**, Nicar**-dipine**, Nife-**dipine and **Nisol**-dipine.

MECHANISM OF ACTION (Fig 10.3.7)

Activation of calcium channel on SA node of the heart leads to increase in force of contraction and also increases electrical conduction resulting in increased heart rate. Similarly activation of calcium channels on blood vessel leads to vasoconstriction.

- Calcium channel blockers blocks calcium channels on vascular smooth muscle they reduce contraction of the arteries and cause an increase in arterial diameter, a phenomenon called vasodilation (CCBs do not work on venous smooth muscle)

- Calcium channel blockers blocks calcium channels on cardiac muscles (myocardium), they reduce the force of contraction of the heart

- Calcium channel blockers blocks calcium channels on SA node, thus slowing down the conduction of electrical activity within the heart, they slow down the heart beat.

(Fig 10.3.7)

USES

Angina pectoris

DOSE AND ROUTE OF ADMINISTRATION

Verapamil Oral: 40, 80, 120 mg tablets, Oral sustained-release and 120, 180, 240 mg tablets; 100, 120, 180, 200, 240, 300 mg capsules and Parenteral: 2.5 mg/mL for injection

Diltiazem Oral: 30, 60, 90, 120 mg tablets (unlabeled in hypertension), Oral sustained-release 60, 90, 120, 180, 240, 300, 360, 420 mg capsules and Parenteral: 5 mg/mL for injection.

Felodipine Oral extended-release: 2.5, 5, 10 mg tablets

Isradipine Oral: 2.5, 5 mg capsules; 5, 10 mg controlled-release tablets

Nicardipine Oral: 20, 30 mg capsules, Oral sustained-release: 30, 45, 60 mg capsules and Parenteral i.v.: 2.5 mg/mL for injection.

Nifedipine Oral: 10, 20 mg capsules and Oral extended-release: 30, 60, 90 mg tablets

Nisoldipine Oral: 10, 20, 30, 40 mg extended-release tablets

ADVERSE EFFECTS

- Dizziness or light-headedness
- Peripheral edema & Ankle swelling
- Headache
- Flushing or heat sensation
- Transient hypotension
- Nausea
- Constipation
- Bradycardia
- Rash

DRUG INTERACTION

- Verapamil and diltiazem reduce the elimination and increase the blood levels of carbamazepine (antiepileptics) and simvastatin (hypolipidemics). This can lead to toxicity from these drugs.

- Verapamil and diltiazem raise plasma digoxin levels which may lead to digoxin toxicity.

CONTRAINDICATION

- Patients with preexistent bradycardia, conduction defects, or heart failure caused by systolic dysfunction should not be given CCBs, especially the cardiac selective, non-dihydropyridines CCBs like Verapamil and diltiazem.

- Non-dihydropyridines like Verapamil and diltiazem, should not be administered to patients being treated with a beta-blocker because beta-blockers also depress cardiac electrical and mechanical activity and therefore the addition of a CCB augments the effects of beta-blockade.

Nursing Implication

- Obtain drug history
- Always check blood pressure before starting antihypertensive drug for the first time, if BP is below 90 systolic or 60 beats per minute (BPM) hold the drug and notify doctor.
- Avoidance patient to grapefruit juice during the therapy with CCBs as it may affect metabolism.
- Caution the patient that sudden withdrawal of CCBs may exacerbate angina.

B BLOCKERS

DRUGS USED

- **M**etoprolol
- **A**tenolol
- **B**isoprolol

} Selective β_1 blocker

MESSAGE TO STUDENTS: Remember the formula which we saw in the chapter of antihypertensive drug **(chapt).** Just remove **"P"** from "**P.MAB",** and remember **"MAB" as "M**arry **A B**lind**",** which becomes **M**etoprolol, **A**tenolol and **B**isoprolol. Here the names of all the drugs ends with common word **"olol",** you have to remember **Metopr, Aten** and **Biso**, which becomes **Metopr-**olol**, Aten-**olol and **Biso-**prolol.

MECHANISM OF ACTION (Fig 10.3.6)

- **Heart:** Stimulation of β_1 receptors on SA node of the heart will increase heart rate and force of contraction.

  So, β blockers blocks β_1 receptors on SA node of the heart and hence will decrease cardiac contractility (negative inotropic effect) and heart rate (negative chronotropic effect), this reduces cardiac work load and myocardial O_2 demand.

- **Kidney:** Blockade of beta1-receptors inhibits the release of renin from juxta-glomerular cells and thereby reduces the activity of the renin-angiotensin-aldosterone system.
- **Central and peripheral nervous system:** Blockade of beta-receptors in the brainstem and of prejunctional beta-receptors in the periphery inhibits the release of neurotransmitters and decreases sympathetic nervous system activity.

(Fig 10.3.6)

USES

Angina pectoris

DOSE AND ROUTE OF ADMINISTRATION

Metoprolol Oral: 50, 100 mg tablets, Oral sustained-release: 25, 50, 100, 200 mg tablets and Parenteral: 1 mg/mL for injection.

Atenolol Oral: 25, 50, 100 mg tablets and Parenteral: 0.5 mg/mL for IV injection

Bisoprolol Oral: 5, 10 mg tablets

ADVERSE EFFECTS

- Bradycardia caused by β blockers may cause life-threatening bradyarrhythmias in patients with partial or complete AV conduction defects.
- Fatigue, sleep disturbances (including insomnia and nightmares), and depression.
- Sudden or abrupt withdraw of β blockers may lead to rebound hypertension

DRUG INTERACTION

- **Cimetidine + β -blockers:** Decreased metabolism of β -blockers that are cleared primarily by the liver
- Aluminum salts, cholestyramine, and colestipol may decrease absorption of b blockers.

CONTRAINDICATION

Second or Third Degree Heart Block

Nursing Implication

- Obtain drug history
- Always check blood pressure before starting antihypertensive drug for the first time, if BP is below 90 systolic or 60 beats per minute (BPM) hold the drug and notify doctor.

- When patient are taking beta blockers, it is also very important to monitor the changes in lab values such as (protien, BUN and creatinine) which can indicate nephrotic syndrome.
- Advice patient NOT STOP TAKING DRUG SUDDENLY. Doing so may cause tachycardia, dysrythmias, elevated BP, angina and MI.
- If patient is on extended release forms of the drug, advice not to be crushed and taken.

POTASSIUM CHANNEL OPENERS

Nicorandil

MECHANISM OF ACTION (Fig 10.4.8)

- Potassium channel openers opens potassium channel in blood vessel (arteries and veins) and also acts as nitric oxide donor
- Efflux of potassium from cell to extracellular space leading to cellular hyperpolarization
- Nitric oxide (NO) causes activation of guanylyl cyclase and an increase in cGMP
- Increased cGMP, dephosphorylate myosin light chasin kinase which interrupt the interaction of actin-myosin in vascular smooth muscle (especially in veins)
- Dilatation of veins leads to decreased preload and reduce cardiac workload and myocardial O_2 demand.
- In some patients, a redistribution of coronary flow may increase oxygen delivery to ischemic tissue.
- In variant angina, the nitrates and the calcium channel blockers may also increase myocardial oxygen delivery by reversing coronary arterial spasm.

USES

Angina pectoris

DOSE AND ROUTE OF ADMINISTRATION

Oral 5-20 mg twice daily

SIDE EFFECTS

Flushing, headache, nausea and vomiting

DRUG INTERACTION

Potassium channel blocker like sulfonylurea partly antagonize the action of nicorandil

CONTRAINDICATION

Cardiogenic shock, Hypotension and Left ventricular failure

Nursing Implication

- Obtain drug history
- Always check blood pressure before starting antihypertensive drug for the first time, if BP is below 90 systolic or 60 beats per minute (BPM) hold the drug and notify doctor.
- Advice patient that nicorandil may cause dizziness when getting up from lying down or sitting position. Use precaution when changing position to prevent fall.
- Advice patient to avoid activities which require to be alert as nicorandil may impair ability to drive or operate heavy machinery.

MISCELLANEOUS DRUGS

I. FATTY ACID OXIDATION INHIBITORS

- **R**anolazine
- **O**xyphendrine
- **T**rimetazidine

MECHANISM OF ACTION (Fig 10.4.9)

Fatty acid oxidation in myocardium will be done by mitochondrial enzyme long chain 3-ketoacyl-coA-thiolase which needs more oxygen leading to more oxygen demand.

Fatty acid oxidation inhibitors inhibits mitochondrial enzyme long chain 3-ketoacyl-coA-thiolase (LC-3-CAT), thus reducing fatty acid oxidation, thus the glucose metabolism increases which needs less oxygen.

(Fig 10.4.9)

II. HYPOLIPIDEMICS

Statins and other hypolipidemics are very important in the long-term treatment of atherosclerotic disease (See **Chapter 10.7** for details)

CHAPTER 10.5

CONGESTIVE HEART FAILURE AND CARDIOTONICS

HEART FAILURE

Heart failure is a condition where cardiac output is not sufficient to provide the oxygen needed by the body tissues. It means the heart is unable to pump sufficient blood as needed by the periphery.

TYPES OF HEART FAILURE

- High output failure
- Low output failure

High output failure

Here the cardiac output will be normal, but the peripheral demand will be more than the normal in some primary disease conditions like hyperthyroidism, beriberi, anemia and arteriovenous shunts.

Here the treatment should be for the primary disease and not for the heart or its functions.

Low output failure

Here the peripheral demand will be normal, but the heart will be unable to pump sufficient blood as needed by the periphery in some condition like coronary artery disease, myocardial infarction etc.

In this kind of heart failure, the cardiotonics are useful which increases the cardiac output without increasing cardiac work load.

Pathophysiology of cardiac failure (low output failure)

When cardiac contractility reduces due to conditions like coronary artery disease, myocardial infarction etc, immediately sympathetic nervous system gets stimulated leading to following adjustment in body mechanism to compensate the low output as follows

- Vasoconstriction of the peripheral blood vessel that increases blood pressure due to action of sympathetic neurotransmitter on α_1 receptor on blood vessel.

- Constriction of vein leads to increase in preload to heart and arteriolar constriction leads to increase of afterload to heart.
- Vasoconstriction of renal blood vessel leading to reduced glomerular filtration rate (GFR) due to action of angiotensin II
- Sodium and water retention due to action of aldosterone (mineralocorticoid).

COMPENSATED HEART FAILURE (Fig 10.5.1)

If the above said adjustments maintain the cardiac output, then it is called as compensated heart failure.

DECOMPENSATED HEART FAILURE (Fig 10.5.1)

But, the above said adjustment cannot maintain the cardiac output for longer time, as a result the cardiac output again gets reduced with increased in the wall thickness of left ventricle with less volume. Finally the conditions worsen leading to complication.

(Fig 10.5.1)

PHARMACOTHERAPY OF HEART FAILURE

DRUGS WITH POSITIVE INOTROPIC EFFECTS USED IN HEART FAILURE

- **CARDIOTONICS**

1. **Cardiac glycosides or Cardenolides:** Digitalis

2. **Sympathomimetics :** Dopamine and dobutamine

3. **Phosphodisterase inhibitors: Bipyridines** like Inamrinone (previously called amrinone) and milrinone.

DRUGS WITHOUT POSITIVE INOTROPIC EFFECTS USED IN HEART FAILURE

1. **DIURETICS:**

- **Loop diuretics / high efficacy or high ceiling diuretics**

a) **F**urosemide

b) **T**orasemide

- **Thiazides diuretics**

a) **H**ydrochlorothiazide

b) **H**ydroflumethiazide

- **Potassium (k^+) sparing diuretics:**

a) **Aldosterone antagonist like** Spironolactone

2. ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACE INHIBITOR):

a) **C**aptopril
b) **E**nalapril

3. ANGIOTENSIN RECEPTOR ANTAGONISTS (AT1 ANTAGONIST OR BLOCKER):

a) **L**osartan
b) **I**rbesartan
c) Candesartan

4. VASODILATORS:

a) **H**ydralazine
b) **I**sosorbide Dinitrate

5. BETA ADRENOCEPTOR BLOCKERS OR β RECEPTOR ANTAGONIST

- Propranolol (Non selective β blocker)
- Metoprolol
- Atenolol } Selective β_1 blocker
- Bisoprolol

DRUGS <u>WITH</u> POSITIVE INOTROPIC EFFECTS USED IN HEART FAILURE

CARDIOTONICS

Cardiotonic are the drugs that affect the intracellular calcium levels of heart muscle, leading to increased contractility (ionotropic effect) which increases cardiac muscle contraction and increases cardiac output.

Cardioronic drugs are called as ionotropic drugs as they increase the force of contraction of the cardiac muscle.

Three groups of cardiotonic agents are available:

CARDIAC GLYCOSIDES OR CARDENOLIDES
DIGITALIS

Digitalis is the name of the genus among plants from which we get cardiac glycosides**, eg, digoxin.**

Source: *Digitalis purpurea*

MECHANISM OF ACTION

First we should understand what happens in cardiac muscle during contraction, then we can understand mechanism of action of Digitalis.

Normal Cardiac Contractility (Fig 10.5.2)

- During action potential, a small amount of calcium enters the cardiac muscle
- This leads to opening of calcium channel on sarcoplasmic reticulum which releases large amount of stored calcium from sarcoplasmic reticulum.
- The released calcium from sarcoplasmic reticulum will lead to interaction of calcium with the actin-troponin-tropomyosin resulting in cardiac muscle contraction (ionotropic effect) during systole. Thus intracellular calcium level is very important which determines the cardiac contractility
- After contraction, the calcium will be taken back to sarcoplasmic reticulum via calcium uptake transporter to maintain free intracellular low level of calcium.
- Due to Sodium-Calcium Exchanger (Na^+/Ca^{2+}) in the cell membrane of cardiac muscle will move the calcium from cytoplasm to extracellular space in exchange with sodium.
- Due to activity of Na^+/K^+ ATPase in the cell membrane of cardiac muscle will finally remove Na^+ from the cell to extracellular space in exchange with K^+ that enter the cell.

(Fig 10.5.2)

Mechanism of action of digitalis (Fig 10.5.3)

Digitalis action can be divided as cardiac and extra-cadrdiac effects

Cardiac effects

- Digitalis inhibits Na^+/K^+ ATPase and this leads to trapping of Na^+ inside the cell.

- This leads to reverse action of Sodium-Calcium Exchanger (Na^+/Ca^{2+}) in the cell membrane of cardiac muscle which removes the Sodium from the cell to extracellular space in exchange with calcium which enters the cardiac cell from extracellular space.

- As I have already told that , a small increase in cellular level of calcium will lead to release of large amount of calcium from the sarcoplasmic reticulum, thus favoring interaction of calcium with the actin-troponin-tropomyosin resulting in cardiac muscle contraction (ionotropic effect) during systole.

- This finally leads to increased cardiac output without much workload to heart.

(Fig 10.5.3)

Extra-cardiac effects

Inhibition of Na^+/K^+ ATPase in other tissues depolarizes and increases spontaneous activity especially in neurons and in smooth muscle cells.

GIT: Anorexia, nausea, vomiting, and diarrhea. It is partially due to direct effects on the smooth muscle gastrointestinal tract and also partially due to central nervous system actions, including chemoreceptor trigger zone (CTZ) stimulation which is main reason for nausea and vomiting.

Central nervous system: Disorientation and hallucinations

Note: Either due to peripheral estrogenic action or hypothalamic stimulation it may rerely lead to Gynecomastia (development of breast in males)

USES

Congestive heart failure

DOSE AND ROUTE OF ADMINISTRATION

Oral: 0.125, 0.25 mg tablets; 0.05, 0.1, 0.2 mg capsules*; 0.05 mg/mL elixir

Parenteral: 0.1, 0.25 mg/mL for i.v injection

Daily dose (slow loading or maintenance) 0.25 (0.125–0.5) mg

Rapid digitalizing dose (rarely used) 0.5–0.75 mg every 8 hours for three doses

SIDE EFFECTS

Anorexia,
Nausea & vomiting
Diarrhea

ADVERSE EFFECTS AND TOXICITY

Anorexia,
Nausea & vomiting
Diarrhea
Cardiac arrhythmia
Visual disturbances

TREATMENT AND ANTIDOTE FOR DIGITALIS TOXICITY

- Electrolyte status should be corrected, if found abnormal
- If patient is not responding within few hours, then check the plasma level of Calcium, magnesium and potassium
- In case of initial ventricular depolarizations or brief runs of bigeminy (arrhythmia), oral potassium supplementation and withdrawal of the glycoside is sufficient.
- In serious arrhythmia due to digitalis, parenteral potassium with other antiarrhythmic drug like lidocaine is preferred.
- In severe digitalis intoxication, insertion of a temporary cardiac pacemaker catheter and administration of digitalis antibodies (digoxin immune fab) is the treatment of choice.

Digoxin immune fab (ovine) (digibind, digifab)

- Parenteral: 38 or 40 mg per vial with 75 mg sorbitol lyophilized powder to reconstitute for IV injection.

- Each vial will bind approximately 0.5 mg digoxin or digitoxin.

DRUG INTERACTION

- Loop diuretics or thiazides or carbonic anhydrase inhibitors cause hypokalemia and hence enhances the toxicity of digitalis.

- K^+ suppliments or potassium sparing diuretics reduces the effect of digitalis

- Calcium supplements + digitalis: increased calcium overload in cardiac muscle and increases digitalis toxicity.

CONTRAINDICATIONS

- Patients having hypokalemia or in those who are on loop diuretics or thiazides or carbonic anhydrase inhibitors which may cause hypokalemia and hence enhances the toxicity of digitalis.

- Patients having hypercalcaemia as increased calcium overload in cardiac muscle and increases digitalis toxicity.

Nursing implication

SYMPATHOMIMETICS

DRUG USED

- Dopamine (catecholamine)

- Dobutamine (non catecholamine)

These drugs are sympathomimetic or β adrenoreceptor agonist

MECHANISM OF ACTION (Fig 10.5.4)

Dopamine is given as i.v infusion and has has dose dependant action as follows

Dopamine

↓

i.v infusion at low dose of 1-5µg/kg/min→ acts on D_1 receptor on renal blood vessel→ renal vasodilatation →increases GFR (improves congestive heart failure)

↓

i.v infusion at therapeutic dose 5-10µg/kg/min→also acts on β_1 receptor SA node of the heart→ increases cardiac contraction (ionotropic effect) and increases cardiac output (improves congestive heart failure)

↓

i.v infusion at high dose of >10µg/kg/min→ acts on α_1 receptor on renal blood vessel→ renal vasoconstriction → decreases GFR (worsens congestive heart failure)

(Fig 10.5.4)

Note: Dobutamine does not act on D_1 receptor on renal blood vessel

USES

Congestive heart failure

DOSE AND ROUTE OF ADMINISTRATION

Dobutamine (most commonly used): Parenteral: 12.5 mg/mL for IV infusion

Dopamine: Parenteral: 40, 80, 160 mg/mL for IV injection; 80, 160, 320 mg/dL in 5% dextrose for IV infusion

ADVERSE EFFECTS

- i.v infusion at high dose of >10µg/kg/min → acts on α1 receptor on renal blood vessel→renal vasoconstriction → decreases GFR (worsens congestive heart failure)

DRUG INTERACTION

CONTRAINDICATION

Nursing implication

PHOSPHODISTERASE INHIBITORS

DRUGS USED

Bipyridines like

- Inamrinone (previously it was called amrinone)
- Milrinone

MECHANISM OF ACTION (Fig 10.5.5)

- We know that when β_1 receptors in the SA node of the heart gets stimulated , then it leads to increased heart rate (chronotropis effect) and increased force of contraction (ionotropic effect).
-
- This effect is due to increase in cellular cAMP level. But cAMP will soon get degraded by an enzyme called *Phosphodisterase* (PDE_3)
- So, *Phosphodisterase* (PDE_3) inhibitors inhibit enzyme *Phosphodisterase* in cardiac muscle, as a result the cAMP cannot get degraded, hence it increases force of contraction of cardiac muscle.

(Fig 10.5.5)

USES

Only for acute heart failure or for an exacerbation of chronic heart failure

DOSE AND ROUTE OF ADMINISTRATION

Inamrinone **:** single intravenous bolus dose of Inamrinone of 0.75 mg/kg to 3 mg/kg

Milrinone**:** 50 mcg/kg loading dose by i.v push over 10 minutes, then 0.375-0.75 mcg/kg/min IV, Maintenance: 1.13 mg/kg/day

ADVERSE EFFECTS

- Inamrinone : Nausea and vomiting; arrhythmias, thrombocytopenia, and changes in liver enzyme
- Milrinone: Arrhythmias.

DRUG INTERACTION

Inamrinone + disopyramide may lead to severe hypotension

CONTRAINDICATION

Severe obstructive cardiomyopathy, hypovolemia, tachycardia, and ventricular aneurysm. Breast feeding

Nursing implication

- Monitor electrolytes, renal function and blood pressure.
- Patients should be monitored by telemetry when on milrinone infusions.
- Infusion site reactions have been reported and may cause milrinone

DRUGS WITHOUT POSITIVE INOTROPIC EFFECTS USED IN HEART FAILURE

DIURETICS

- Diuretics are the drugs that help in excretion of large amount of sodium and water through urine thus reducing the sodium and water load in the blood.
- Diuretics lower or antagonize ADH action are diuretic.

We will study normal event that takes place in each segment followed by the drugs acting in each segment

EVENTS THAT TAKES PLACE IN PCT AND DRUGS ACTING ON IT

- Sodium bicarbonate, sodium chloride, glucose, amino acids, and other organic solutes are reabsorbed with the help of specific transport systems in the early part of proximal tubule.
- Reabsorption of sodium bicarbonate and sodium chloride are very important which plays important role in body fluid volume.
- There is no drug acting at this side to inhibit reabsorption of sodium chloride, but there are drugs that can inhibit sodium bicarbonate reabsorption at this site.
- Let us see how sodium bicarbonate is absorbed by normal mechanism.

Before you try to know complete events that takes place in each segment, I will give you an idea about how understand.

First let us divide the event that is taking place under three headings

- **Event in tubular lumen (including luminal membrane)**
- **Event in tubule (including the tubular membrane) and**
- **Event in interstitial blood**

Note: The same pattern will be followed to study the drugs acting on other segments also ok…

A. REABSORPTION OF SODIUM BICARBONATE AT EARLY PART OF PROXIMAL TUBULE (Fig 7.3)

4. Event in tubular lumen (including luminal membrane)

Let us start with luminal urine containing sodium bicarbonate ($NaHCO_3$) which has come from blood ok…

- The sodium (Na^+) from sodium bicarbonate from the tubular lumen gets absorbed in to proximal tubular cell in exchange with hydrogen (H^+) via Na^+/H^+ exchanger.

- Hydrogen (H^+) which is in the tubular lumen now combines with bicarbonate (HCO_3^-) to form carbonic acid (H_2CO_3).

- Carbonic acid (H_2CO_3) is highly unstable and gets split into water (H_2O) and carbondioxide (CO_2) by an enzyme present on luminal membrane called as luminal *Carbonic anhydrase* (CAs).

- Carbondioxide (CO_2) from the lumen diffuses to tubular cell

5. Event in tubular cell (including the tubular membrane)

- The sodium (Na^+) which gets absorbed in to proximal tubule in exchange with hydrogen (H^+) via Na^+/H^+ exchanger will be go to interstitial blood in exchange with potassium (K^+) via Na^+/K^+ ATP ase.

- Carbondioxide (CO_2) from the lumen that diffuses to tubular cell gets combined to cellular water (H_2O) to form carbonic acid (H_2CO_3).

- Here also the formed cellular carbonic acid (H_2CO_3) is unstable and gets split to hydrohen (H^+) and bicarbonate (HCO_3^-) by an enzyme present towards cell called as cellular *Carbonic anhydrase* (CAs).

- Hydrogen (H^+) gets to tubular lumen in exchange with sodium (Na^+) via Na^+/H^+ exchanger

- Bicarbonate (HCO_3^-) from the tubular cell goes to interstitial blood via transporter.

6. Event that takes place in interstitial blood

Sodium (Na^+) and bicarbonate (HCO_3^-) which is in the interstitial blood gets combined to form sodium bicarbonate ($NaHCO_3$)

Please recall that we have started with sodium bicarbonate ($NaHCO_3$) in the luminal urine and ended with sodium bicarbonate ($NaHCO_3$) in the interstitial blood. This is how the sodium bicarbonate ($NaHCO_3$) gets absorbed from urine to blood.

DRUGS ACTING ON EARLY PART OF PROXIMAL TUBULE

CARBONIC ANHYDRASE (CAs) INHIBITORS

DRUGS USED

- **A**cetazolamide
- **B**rinzolamide
- **D**orszolamide

MESSAGE TO STUDENT: Formula to remember *Carbonic anhydrase* (CAs) inhibitors is **"ABD",** you can remember as "**After Birth Day",** which becomes **A**cetozolamide, **B**rinzolamide and **D**orzolamide. Here the last word of all the drugs ends with **"Zolamide"** and you have to remember **Aceta, Brin and Dor,** which finally becomes **Aceto-**zolamide, **Brin-**zolamide **and Dor-**zolamide.

MECHASNISM OF ACTION

- Now our aim is to prevent sodium bicarbonate absorption. Fortunately we have a drug that act at this site called as *Carbonic anhydrase* (CAs) inhibitors

- *Carbonic anhydrase* (CAs) inhibitors inhibit enzyme luminal *Carbonic anhydrase* (CAs) and hence prevent bicarbonate reabsorption (**Fig 7.4)**

(**Fig 7.4)**

USES

As more and more bicarbonate which is not absorbed and remains in the urine, it may increase luminal pH and decrease blood pH leading to metabolic acidosis which is very dangerous, hence

Carbonic anhydrase (CAs) inhibitors even though has diuretic property but usually are not used for diuretic purposes.

OTHER USES

- **Urinary Alkalinization:** As it inhibits bicarbonate reabsorption and increase luminal pH, *Carbonic anhydrase* (CAs) inhibitors are used as Urinary Alkalinizer.

This is very useful to remove any poisonous acidic drugs which may get absorbed if urine is also acidic. But alkalinization of urine makes acidic drugs to get ionized and hence its excretion increases in urine.

- **Glaucoma:** It is a condition where there is increased intra ocular pressure due to excess aqueous humour production or decreased drainage. For the production of aqueous humour sodium bicarbonate is needed and it gets secreted in the same way as it occurs in renal tubule.

Carbonic anhydrase (CAs) inhibitor inhibits *Carbonic anhydrase* enzyme and decrease the production of aqueous humour.

- **Acute Mountain Sickness:**

Formation of cerebrospinal fluid (CSF) needs sodium bicarbonate which has the same mechanism as we saw in the renal tubule. When a person climbs suddenly to a high altitude, the formation of CSF increases and pH of CSF also increases. This leads to acute mountain sickness with symptoms like Weakness, dizziness, insomnia, headache, and nausea.

Carbonic anhydrase (CAs) inhibitors inhibit *Carbonic anhydrase* and decrease the production of formation of CSF and decrease pH of CSF.

- **Metabolic Alkalosis**

Metabolic alkalosis is an increase in blood pH which can be dangerous in patient with heart disease and decrease in blood pH can be life saving.

Carbonic anhydrase (CAs) inhibitors prevents reabsorption of sodium bicarbonate and decrease blood pH, thus can be very useful in metabolic alkalosis.

DOSE AND ROUTE OF ADMINISTRATION

Acetazolamide

Oral: 125, 250 mg tablets

Oral sustained-release: 500 mg capsules

Brinzolamide

Ophthalmic: 1% suspension

Dorzolamide

Ophthalmic: 2% solution

ADVERSE EFFECTS

Hyperchloremic Metabolic Acidosis

Renal Stones

DRUG INTERACTION

Acetazolamide + potassium-sparing diuretics: increased metabolic acidosis and hyperkalemia

Acetazolamide + Quinidine: Acetazolamide decreases excretion of Quinidine by increasing urinary pH.

CONTRAINDICATIONS

Liver cirrhosis

Nursing Implication

- Assess for allergy and contraindications: allergy to sulfa, severe renal or hepatic disease
- Monitor for adverse drug reaction and inform doctor if any.
- Assess daily weight, fluis Input & urine Output , serum

B. REABSORPTION OF WATER FROM LATE PCT AND DESCENDING LIMB OF HENLE'S LOOP

- Late part of the PCT and descending limb of henle's loop is highly permeable to water and large amount of water can get absorbed from this segment.
- So any drug that prevent water absorption from this segment will lead to excess of water loss in urine as no other portion of the nephron is permeable. (**Fig 7.5)**
- So any drug that prevents the water reabsorption at this segment due to osmotic effect can be a good diuretic.

(Fig 7.5)

DRUGS ACTING ON PCT AND DESCENDING LIMB OF HENLE'S LOOP

OSMOTIC DIURETICS

DRUGS USED

Mannitol

MESSAGE TO STUDENT: Formula to remember the drug under osmotic diuretics is **"O",** are you confused? Here **"O"** means osmotic diuretics and mannitol also has the word **"O".** You split the word and remember as **"Man-ni-tOl"**

MECHASNISM OF ACTION

- It is an impermeant solute which is only filtered, but neither secreted nor reabsorbed.
- Once inside the tubular lumen, then it even if water tries to get absorbed then the concentration of the solute increases and prevents further water reabsotption due to osmotic effect.
- Once the water does not get absorbed at this segment due to effect of osmotic diuretic, it cannot get absorbed in other segment as well also as they are not permeable to water. Hence osmotic diuretics lead to excretion of more water than other solutes. This is called as water dieresis. (**Fig 7.6)**

(Fig 7.6)

USES

Anuria or oliguria: It is a condition where urine is not formed properly or its volume is reduced. Mannitol is useful in these conditions

Reduction of Intracranial and Intraocular Pressure: In these the intracellular fluid increases which may lead to complication. Mannitol reduces intracranial and intraocular pressure.

DOSE AND ROUTE OF ADMINISTRATION

Parenteral: 5, 10, 15, 20, 25% for i.v injection

To decrease intracranial pressure: A dose of 1–2 g/kg mannitol is administered intravenously.

ADVERSE EFFECTS

Extracellular Volume Expansion: Due to extraction of water from the cell leads to Headache, nausea, and vomiting

Dehydration and Hypernatremia: Due to extreme water loss in urine and increased sodium in blood

DRUG INTERACTION

Mannitol + Lithium (antimanic): Increased urinary excretion of lithium

CONTRAINDICATIONS

- In heart failure and pulmonary congestion, it may cause pulmonary oedema.
- Liver dysfunction, Oliguria due to renal disease and patient suffering from intracranial bleeding.

NURSING IMPLICATION

- Some oliguric patients do not respond to an osmotic diuretic. Therefore, a test dose of mannitol (12.5 g intravenously) should be given prior to starting a continuous infusion.
- Mannitol should not be continued unless there is an increase in urine flow rate to more than 50 mL/h during the 3 hours following the test dose.
- Mannitol (12.5–25 g) can be repeated every 1–2 hours to maintain urine flow rate greater than 100 mL/h.
- Prolonged use of mannitol is not advised.

C. REABSORPTION OF SODIUM CHLORIDE (Nacl) FROM THICK ASCENDING LIMB (Fig 7.7)

1. Event in tubular lumen (including luminal membrane)

- Sodium chloride (NaCl) present in the luminal urine reaches lumen of thick ascending limb.
- A symporter called Sodium-Potassium-2 Chloride ($Na^+/K^+/2Cl^-$) present on the luminal membrane operates and helps in the absorption of Sodium, Potassium and Chloride in to tubular cell.

2. Event in tubular cell (including the tubular membrane)

- The sodium (Na^+) which gets absorbed in to tubular cell will be go to interstitial blood in exchange with potassium (K^+) that comes to tubular cell from interstitial blood via Na^+ / K^+ ATP ase .
- The chloride (Cl^-) also enters interstitial blood from tubular cell by the help of other transporter.

3. Event that takes place in interstitial blood

- The sodium (Na^+) and chloride (Cl^-) combines in interstitial blood to form NaCl.

- Please recall that we have started with sodium chloride (NaCl) in the luminal urine of thick ascending limb and ended with sodium chloride (NaCl) in the interstitial blood. This is how the sodium chloride (NaCl) gets absorbed from urine to blood. About 35-40% of sodium gets absorbed at this segment.

(Fig 7.7)

Note:

The potassium (K+) that has entered the tubular cell from the lumen of thick ascending limb due to action of $Na^+/K^+/2Cl^-$ and the potassium (K+) that has entered from interstitial blood to tubular cell will increase intracellular potassium (K+) level.

So, the increased intracellular potassium (K+) will back diffuse to tubular lumen of thick ascending limb, thus the luminal potassium (K+) level increase.

Increased luminal potassium (K+) level will favors for re-absorption of calcium ($Ca2^+$) and Magnesium (Mg2+) from tubular lumen to interstitial blood via paracellular pathway.

DRUGS ACTING ON THICK ASCENDING LIMB

LOOP DIURETICS / HIGH EFFICACY OR HIGH CEILING DIURETICS

DRUGS USED

Furosemide

Torsemide

MESSAGE TO STUDENTS : Formula to drugs under loop diuretics is **"FT",** you can remember as "Fine Touch", which becomes **F**urosemide and **T**orsemide. Here the names of both the drugs ends with common word "semide", you have to remember "Furo and Tor", which becomes **F**uro-semide and **T**or-semide

MECHANISM OF ACTION

Loop diuretics inhibit $Na^+/K^+/2Cl^-$ symporter and mainly prevent the absorption of Sodium ($Na^{+)}$ and chloride (Cl^-) along with inhibition of absorption of K^+.

Maximum absorption of sodium can be prevented by inhibiting $Na^+/K^+/2Cl^-$ symporter. **(Fig 7.8)**

(Fig 7.8)

USES

- Hypertesion
- Hyperkalemia
- Heart failure
- Acute pulmonary edema and other edematous conditions
- Acute renal failure
- Acute hypercalcemia
- Anion disease

MESSAGE TO STUDENTS : Formula to remember uses of loop diuretics are 3H and 3A, which becomes **H**ypertesion, **H**yperkalemia, **H**eart failure, and **A**cute pulmonary edema and other edematous conditions, **A**cute renal failure and **A**cute hypercalcemia

DOSE AND ROUTE OF ADMINISTRATION

Oral Furosemide 20–80 mg (Furosemide i.v is also available (8 mg/mL solutions))

Oral Torsemide 2.5–20 mg

ADVERSE EFFECTS

- Allergic Reactions
- Hypokalemia (decreased serum K^+ level)
- Hypomagnesemia (decreased serum Mg^+ level)
- Hypocalcaemia (decreased serum Ca^{2+} level)

Note: You may think why Hypokalemia (decreased serum K^+ level), Hypomagnesemia (decreased serum Mg^+ level) and Hypocalcaemia (decreased serum Ca^{2+} level) occurs when loop diuretics are given.

Reason for Hypomagnesemia (decreased serum Mg^+ level) and Hypocalcaemia (decreased serum Ca^{2+} level)

- Please recall that he potassium (K+) that has entered the tubular cell from the lumen of thick ascending limb due to action of $Na^+/K^+/2Cl^-$ and the potassium (K+) that has entered from interstitial blood to tubular cell will increase intracellular potassium (K+) level.

- So, the increased intracellular potassium (K+) will back diffuse to tubular lumen of thick ascending limb, thus the luminal potassium (K+) level increase.

- Increased luminal potassium (K+) level will favors for re-absorption of calcium ($Ca2^{+}$) and Magnesium (Mg2+) from tubular lumen to interstitial blood via paracellular pathway.

- So if you inhibit $Na^{+}/K^{+}/2Cl^{-}$ symporter then intracellular potassium will not increase and hence potassium will not back diffuse and there will be no luminal positive potential, hence Mg^{+} and Ca^{2+} does not get absorbed leading to hypomagnesaemia (decreased serum Mg^{+} level) and Hypocalcaemia (decreased serum Ca^{2+} level)

Reason for Hypokalaemia (decreased serum K^{+} level)

- When absorption of sodium prevented in thick ascending limb by inhibiting $Na^{+}/K^{+}/2Cl^{-}$ symporter, more sodium reaches collecting duct where sodium gets absorbed via sodium channel with secretion of potassium in to collecting duct which gets finally excreted in urine, thus leading to hypokalaemia.

- Hence loop diuretics are combined with potassium sparing diuretics to prevent potassium loss.

DRUG INTERACTION

NSAIDs + Loop diuretics: Efficacy of loop diuretic gets reduced

Bile acid-binding resins + Loop diuretics: Decreased absorption of Loop diuretics

CONTRAINDICATION

History of allergy to the drug

In Hepatic cirrhosis or renal failure, or heart failure

NURSING IMPLICATION

- Obtain history of drug allergy
- Monitor the condition of the patient for the response
- Check the lab report and correlate with clinical response
- Check for the signs of dehydration
- Furosemide i.v should be given slowly, not faster than 20 mg/min
- Evaluate signs of ototoxicity
- Don't administer furosemide concurrently with aminoglycoside (e.g. gentamicin) which also is ototoxic

D. REABSORPTION OF SODIUM CHLORIDE (NaCl) FROM DISTAL CONVOLUTED TUBULE . (**Fig 7.9)**

1. Event in tubular lumen (including luminal membrane)

NaCl in the luminal urine present in the **distal convoluted tubule** is reabsorbed via sodium chloride symporter present on the luminal membrane.

2. Event in tubular cell (including the tubular membrane)

The sodium (Na^+) which gets absorbed in to tubular cell will be go to interstitial blood in exchange with potassium (K^+) that comes to tubular cell from interstitial blood via Na^+ / K^+ ATP ase .

The chloride (Cl^-) also enters interstitial blood from tubular cell by the help of other transporter.

3. Event that takes place in interstitial blood

The sodium (Na^+) and chloride (Cl^-) combines in interstitial blood to form NaCl.

. (Fig 7.19)

DRUGS ACTING ON DISTAL CONVOLUTED TUBULE

THIAZIDES DIURETICS

DRUGS USED

Hydrochlorothiazide

Hydroflumethiazide

MESSAGE TO STUDENT: Formula to remember the drug under thiazides is **"HH",** The starting name and ending name of both the drugs are **"Hydro"** and **"thiazide".** You have to remember the middle word as **"chloro"** and **"flume",** which becomes **Hydro-chloro-thiazide** and **Hydro-flume-thiazide**

MECHANISM OF ACTION

Thiazide diuretics inhibit Na^+/Cl^- symporter and mainly prevent the absorption of Sodium ($Na^{+)}$ and chloride (Cl^-). **(Fig 7.10)**

(Fig 7.10)

USES

- Hypertension
- Diabetes Insipidus
- Nephrolithiasis (due to calcium)

DOSE AND ROUTE OF ADMINISTRATION

Hydrochlorothiazide 25–100 mg As single dose

Hydroflumethiazide 25–100 mg In two divided doses

ADVERSE EFFECTS

Allergic Reactions

Hypokalemia (decreased serum K^+ level)

Hyperglycemia

Hyperlipidemia

Reason for Hypokalaemia (decreased serum K^+ level)

- When absorption of sodium is prevented in thick ascending limb by inhibiting Na+/K+/2Cl^- symporter, more sodium reaches collecting duct where sodium gets absorbed via sodium channel with secretion of potassium in to collecting duct which gets finally excreted in urine, thus leading to hypokalaemia.

- Hence thiazides diuretics are also are combined with potassium sparing diuretics to prevent potassium loss.

DRUG INTERACTION

CONTRAINDICATION

NURSING IMPLICATION

- Obtain history of drug allergy
- Monitor the condition of the patient for the response
- Check the lab report and correlate with clinical response
- Check for the signs of dehydration

D. REABSORPTION OF SODIUM (Na^+) AND SECRETION OF POTASSIUM (K^+) FROM COLLECTING DUCT

- We already know that when absorption of sodium is prevented in thick ascending limb by inhibiting Na+/K+/2Cl^- symporter or by inhibiting Na+/ Cl^- symporter in distal convolute tubule, then more sodium reaches collecting duct where sodium gets absorbed via sodium channel with secretion of potassium in to collecting duct which gets finally excreted in urine, thus leading to hypokalaemia.

- When more sodium reaches collecting duct, Aldosterone (mineralocorticoid) diffuses in to tubular cell from interstitial blood and binds to aldosterone receptors in the tubular cell.

- Aldosterone and aldosterone receptor forms a complex and translocates to nucleus and binds to specific element of DNA. (**Fig 7.11)**

(Fig 7.11)

- DNA synthesis mRNA which directs ribosomes to synthesis a protein called Aldosterone induced protein (AIP).

- Aldosterone induced protein (AIP) will stimulate sodium channel in the collecting duct and causes sodium absorption in exchange with potassium secretion in to collectinh duct from tubular cell.

- Thus more the sodium reaches the collecting duct, more the sodium absorption from collecting duct and more the potassium secretion into luminal urine which gets excreted leading to hypokalaemia.

DRUGS ACTING ON COLLECTING DUCT

POTASSIUM (K^+) SPARING DIURETICS

ALDOSTERONE ANTAGONIST: Spironolactone

SODIUM CHANNEL BLOCKERS: Amiloride and **T**riampterene

ALDOSTERONE ANTAGONIST

DRUGS USED

Spironolactone

MECHANISM OF ACTION

Spironolactone antagonizes aldasterone and hence inhibits sodium absorption (Na^+) and potassium (K^+) secretion. (**Fig 7.12)**

(**Fig 7.12)**

USES

Given along with furosemide or thiazide in hypertension to prevent hypokalaemia induced by furosemide or thiazide

Hyperaldosteronism condition like Conn's syndrome, ectopic ACTH production) or to secondary aldosteronism (from heart failure, hepatic cirrhosis, nephrotic syndrome)

DOSE AND ROUTE OF ADMINISTRATION

Oral: 25, 50, 100 mg tablets

Dose : 50–100 mg/day

ADVERSE EFFECTS

- Hyperkalemia
- Hyperchloremic Metabolic Acidosis
- Gynecomastia
- Acute Renal Failure
- Kidney Stones

DRUG INTERACTION

ACE inhibitors

Concomitant administration of ACE inhibitors with potassium-sparing diuretics has been associated with severe hyperkalemia.

Alcohol, barbiturates, or narcotics

Potentiation of orthostatic hypotension may occur.

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalemia, may occur. Alcohol, Milk product containing potassium and high salt diet

CONTRAINDICATION

Contraindicated for patients with anuria, acute renal insufficiency, significant impairment of renal excretory function, or hyperkalemia.

Nursing Implication

- Check blood pressure before initiation of therapy and at regular intervals throughout therapy.
- Lab tests: Monitor serum electrolytes (sodium and potassium) especially during early therapy; monitor digoxin level when used concurrently.
- Assess for signs of fluid and electrolyte imbalance, and signs of digoxin toxicity.
- Monitor daily Input & Output and check for edema. Report lack of diuretic response or development of edema; both may indicate tolerance to drug.
- Weigh patient under standard conditions before therapy begins and daily throughout therapy. Weight is a useful index of need for dosage adjustment. For patients with ascites, physician may want measurements of abdominal girth.
- Observe for and report immediately the onset of mental changes, lethargy, or stupor in patients with liver disease.
- Adverse reactions are generally reversible with discontinuation of drug. Gynecomastia appears to be related to dosage level and duration of therapy; it may persist in some after drug is stopped.
- Be aware that the maximal diuretic effect may not occur until third day of therapy and that diuresis may continue for 2–3 d after drug is withdrawn.
- Report signs of hyponatremia or hyperkalemia, most likely to occur in patients with severe cirrhosis.
- Avoid replacing fluid losses with large amounts of free water (can result in dilutional hyponatremia).
- Weigh 2–3 times each week. Report gains/loss of 5 lb.
- Advice patient to avoid excessive intake of high-potassium foods and salt substitutes.
- Advice patient not to breast feed while taking this drug.

SODIUM CHANNEL BLOCKERS

DRUGS USED

- **A**miloride

- **T**riampterene

MESSAGE TO STUDENT: Formula to remember sodium channel blockers is **"AT",** you can remember as **"After Travel"**, which becomes **Amiloride** and **Triampterene.** You can split the words and remember as **Ami-lo-ride** and **Tri-amp-te-rene**

MECHANISM OF ACTION

We already know that aldosterone action will result in Na^+ re-absorption via sodium channel and increases K^+ secretion via potassium channel.

Sodium channel blockers will block sodium channel in collect duct and prevents Na^+ re-absorption which also prevents potassium secretion in to luminal urine in collecting dust. This will prevent hypokalaemia. **Fig 7.13**

Fig 7.13

USES

- Given along with furosemide or thiazide in hypertension to prevent hypokalaemia induced by furosemide or thiazide.
- Primary hyperaldosteronism.
- In hypokalaemia.

DOSE AND ROUTE OF ADMINISTRATION

Oral Amiloride 5 mg Once daily

Oral Triamterene 50 mg 1–3 times daily

ADVERSE EFFECTS

Headache, dizziness, nausea, vomiting, loss of appetite, abdominal pain or diarrhea may occur.

DRUG INTERACTION

ACE inhibitors or potassium supplement + Sodium channel blockers like amiloride and triampterene : Increases serum potassium level leading to hyperkalaemia

CONTRAINDICATION

- Elevated serum potassium (>5.5 mEq/L)
- Concomitant use of other potassium-sparing diuretics
- In anuria, acute or chronic renal insufficiency; evidence of diabetic nephropathy; or type 1 diabetes mellitus, metabolic or respiratory acidosis and hepatic function impairment.

NURSING IMPLICATION

- Monitor for Signs & Symptoms of hyperkalemia and hyponatremia .
- Lab tests: Serum potassium levels should be monitered, particularly when therapy is initiated, whenever dosage adjustments are made, and during any illness that may affect kidney function.

- Intermittent evaluations of Blood Urea Nitrogen , creatinine, and ECG for patients with renal or hepatic dysfunction, diabetes mellitus, older adults, or the debilitated should be done.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACE INHIBITORS)

DRUG USED

Captopril

Enalapril

MESSAGE TO STUDENTS: Formula to remember the drugs used as angiotensin-converting enzyme inhibitors (ACE inhibitors) as **"CE",** you can remember as **"C**hemical **E**ngineer**",** which becomes **C**aptopril and **E**nalapril. Here the names of both the drugs ends with common words as **"pril",** you have to remember "Capto" and "Enala". Now remember as "**Capto-** pril" and "**Enala-** pril".

Other drugs used as ACE inhibitors are **Rami-**pril **, Lisino**-pril, **Fosino**-pril **, Benaze**-pril, **Moexi**-pril, **Perindo**-pril**, Quina**-pril, , and **Trandola**-pril.

Note: Here also the name of all the drugs ends with a common word as **"pril"**

MECHANISM OF ACTION

Already we know the role of angiotensin converting enzyme for increase of blood pressure

- Following factors stimulate **Renin** release from the kidney

    e) Reduced renal arterial pressure
    f) Sympathetic stimulation
    g) Reduced sodium delivery or
    h) Increased sodium concentration at the distal renal tubule

- Renin acts upon inactive angiotensinogen to angiotensin I.

- Angiotensin I will be then converted, by endothelial enzyme *Angiotensin converting enzyme* (ACE), to angiotensin II

- Angiotensin II acts on AT1 receptor on blood vessel and leads to has vasoconstrictor

- Angiotensin II acts on adrenal gland and increases aldosterone secretion which retains sodium and water.

- Both vasoconstriction and increased sodium and water leads to increased blood pressure. **(Fig. 10.3.2)**

(Fig. 10.3.2)

- *Angiotensin converting enzyme* inhibitors inhibits *Angiotensin converting enzyme* and prevent the conversion of angiotensin I to angiotensin II, thus it results in vasodilatation and reduces blood pressure.It also increases GFR leading to increased excretion of sodium and water.

USES

Hypertension

OTHER USES

- Congestive heart failure

- Myocardial infarction

DOSE AND ROUTE OF ADMINISTRATION

Captopril : Oral: 12.5, 25, 50, 100 mg tablets

Enalapril : Oral: 2.5, 5, 10, 20 mg tablets

ADVERSE EFFECTS

Dry Cough & Angioedema (due to inhibition of bradykinin degradation) **(Fig. 10.3.3)**

(Fig. 10.3.3)

Skin Rash

- Hypotension : Orthostatic or postural hypotension
- Hyperkalemia
- Acute Renal Failure
- Fetopathic
- Proteinuria

DRUG INTERACTION

- Antacids reduce the oral bioavailability of ACE inhibitors

- K^{+}-sparing diuretics and K+ supplements may exacerbate ACE inhibitor–induced hyperkalemia.

CONTRAINDICATION

- In second trimester of pregnancy

- Bilateral renal artery stenosis.

Nursing Implication

- Obtain a complete health history of the patient including recent cardiac events and any incidence of angioedema, allergies, drug history, and possible drug interactions.
- Always check blood pressure before starting antihypertensive drug for the first time.
- Obtain baseline ECG and vital signs.
- Assess neurological status and level of consciousness.
- Obtain blood and urine specimens for laboratory analysis.
- About the first-dose phenomenon and reassure that this effect diminishes with continued therapy.
- To immediately report feelings of faintness because rapid reduction in blood pressure can cause changes in consciousness.
- To rest in the supine position beginning 1 hour after administration and for 3 to 4 hours after the first dose.

ANGIOTENSIN RECEPTOR ANTAGONISTS (AT$_1$ RECEPTOR BLOCKER (ARBs) OR AT$_1$ RECEPTOR ANTAGONIST)

DRUG USED

Telmisartan
Losartan
Irbesartan
Candesartan

MESSAGE TO STUDENTS: Remember the drugs used as angiotensin receptor blockers or antagonist or AT$_1$ receptor antagonist or ARBs is **"Tell-me - LIC",** you can remember as "**Tel**–

mi- Life **I**nsurance **C**orporation", which becomes **T**elmisartan, **L**osartan , **I**rbesartan and **C**andesartan. The names of the drugs ends with common words as "sartan", you have to remember Losa, Irbe and Cande, which becomes **Telmi**-sartan**, Losa**-sartan, **Irbe**-sartan and **Cande-**sartan.

Other drugs used as angiotensin receptor blockers or antagonist or AT_1 receptor antagonist or ARBs are **val-**sartan and **Epro**-sartan.

MECHANISM OF ACTION

- We already know that Angiotensin II acts on AT1 receptor on blood vessel and leads to has vasoconstrictor.

- Angiotensin receptor antagonists (AT1 antagonist or blocker) blocks Angiotensin receptor and inhibits the action of Angiotensin II acts on AT_1 receptor on vascular smooth muscle.

- It results in vasodilatation and reduces blood pressure.

It also increases GFR due to decreased aldosterone secretion and renal vasodilatation leading to increased excretion of sodium and water. **(Fig. 10.3.4)**

-

(Fig. 10.3.4)

USES

Hypertension in those who experience dry cough & angioedema with ACE inhibitors

OTHER USES

- Congestive heart failure

- Myocardial infarction

DOSE AND ROUTE OF ADMINISTRATION

Telmisartan Oral: 20, 40, 80 mg tablets

Losartan Oral: 25, 50, 100 mg tablets

Irbesartan Oral; 75, 150, 300 mg tablets

Candesartan Oral: 4, 8, 16, 32 mg tablets

ADVERSE EFFECTS

- Teratogenic Potential
- Hypotension
- Oliguria
- Progressive Azotemia (elevation of blood urea nitrogen (BUN) and serum creatinine levels.)
- Acute Renal Failure.
- Hyperkalemia

DRUG INTERACTION

- K^{+}-sparing diuretics and K+ supplements may exacerbate ARBs induced hyperkalemia.

CONTRAINDICATION

- In second trimester of pregnancy

- Bilateral renal artery stenosis.

Nursing Implication

- Always check blood pressure before starting antihypertensive drug for the first time.
- Monitor Blood Urea Nitrogen
- Monitor creatinine and electrolytes
- Tell the patients to report edema in feet and legs daily.
- Monitor hydration status.

VASODILATORS

Vasodilator drugs can be divided into

- **Selective arteriolar dilators : H**ydralazine, **M**inoxidil, **D**iazoxide and **F**enoldopam
- **Venous dilators: N**itrates
- **Arterial and venous dilators : S**odium nitroprusside

SELECTIVE ARTERIOLAR DILATORS

DRUGS USED

- **H**ydralazine

- **M**inoxidil
- **D**iazoxide
- **F**enoldopam

MESSAGE TO STUDENTS: Formula to remember the drug used as selective arteriolar dilators is **"HMDF",** you can remember as **"H**ead **M**aster **D**istant **F**riend**".** which becomes **H**ydralazine, **M**inoxidil, **D**iazoxide and **F**enoldopam. Remember the names of the drugs by splitting the words as **H**ydra-la-zine, **M**in-oxi-dil, **D**ia-zo-xide and **F**en-oldo-pam

MECHANISM OF ACTION

- **H**ydralazine, **M**inoxidil and **D**iazoxiden opens potassium channels in arteolar smooth muscle and stabilizing the membrane potential at the resting level, thus leads to arteolar dilatation.
- **F**enoldopam acts primarily as an agonist of dopamine D_1 receptors in arteolar smooth muscle resulting in dilation of peripheral arteries and natriuresis (increased excretion of sodium).
- Dilatation of peripheral arteries leads to decreased afterload and reduce cardiac workload. **(Fig 10.3.9)**

(Fig 10.3.9)

USES

Congestive heart failure

DOSE AND ROUTE OF ADMINISTRATION

Hydralazine Oral: 10, 25, 50, 100 mg tablets

Minoxidil Oral: 2.5, 10 mg tablets

Diazoxide Oral (Proglycem): 50 mg capsule; 50 mg/mL oral suspension and Parenteral: 15 mg/mL ampule

Fenoldopam Parenteral: 10 mg/mL for IV infusion

ADVERSE EFFECTS

- **H**ydralazine: Headache, nausea, anorexia, palpitations, sweating, and flushing.
- Minoxidil: Headache, sweating, and hirsutis
- Diazoxide: Hypotension

- Fenoldopam: Tachycardia, headache, and flushing

DRUG INTERACTION

- **H**ydralazine + Nonsteroidal anti-inflammatory drugs: Decreased antihypertensive response to hydralazine.
- **M**inoxidil + Calcium channel blockers or central sympatholytics: increased fluid retention
- **D**iazoxide: Since diazoxide is highly bound to serum proteins, it may displace other substances which are also bound to protein, such as bilirubin or coumarin (warfarin- oral anticoagulant) and its derivatives, resulting in higher blood levels of these substances.
- **F**enoldopam iv increases effects of carvedilol oral by added drug effects

CONTRAINDICATION

- Coronary artery disease
- Aortic stenosis
- Mitral stenosis

Nursing Implication

- Advice patient not to discontinue the drug abruptly
- Drug tolerance may develop so keep checking for the drug response
- As these may cause orthostatic hypotension – advice patient to change position slowly
- Inform patients that palpitations may occur during early stages of therapy.
- Monitor the weight of the patient daily.

VENOUS DILATORS

DRUG USED

Nitrates : Isosorbide dinitrate

MECHANISM OF ACTION

- Isosorbide dinitrate is denitrated by *glutathione S-transferase*.

- Free nitrite ion is released, which is then converted to nitric oxide causes activation of *guanylyl cyclase* and an increase in cGMP

- Increased cGMP, dephosphorylate *myosin light chain kinase* (MLCK) which interrupt the interaction of actin-myosin in vascular smooth muscle (especially in veins)

- Dilatation of veins leads to decreased preload and reduce cardiac workload. **(Fig 10.3.10)**

(Fig 10.3.10)

USES

Congestive heart failure

DOSE AND ROUTE OF ADMINISTRATION

Isosorbide dinitrate, oral 10–60 mg per 4–6 hours

ADVERSE EFFECTS

- Orthostatic Hypotension
- Tachycardia
- Throbbing Headache

DRUG INTERACTION

- Increased hypotensive effects with alcohol or vasodilators. Marked orthostatic hypotension may occur when used with calcium channel blockers.
- Vasodilatory effect may be reduced with dihydroergotamine.

CONTRAINDICATION

In case of intracranial pressure

- Obstructive Hypertrophic Cardiomyopathy
- Severe Fluid Deficiency
- Inferior Myocardial Infarction With Right Ventricular Involvement
- Raised Intracranial Pressure
- Cardiac Tamponade.

Nursing Implication

- **History:** Allergy to nitrates, severe anemia, GI hypermobility, head trauma, cerebral hemorrhage, hypertrophic cardiomyopathy, pregnancy, lactation

- **Physical:** Skin color, temperature, lesions; orientation, reflexes, affect; orthostatic BP, baseline ECG, peripheral perfusion, adventitious sounds, liver evaluation, normal output.

- Give oral preparations on an empty stomach, 1 hr before or 2 hr after meals; take with meals if severe, uncontrolled headache occurs.

- Keep life support equipment readily available if overdose occurs or cardiac condition worsens.

- You may experience these side effects: Dizziness, light-headedness (may be transient; use care to change positions slowly) and headache

- Report blurred vision, persistent or severe headache and rash.

ARTERIAL AND VENOUS DILATORS

DRUG USED

Sodium nitroprusside

MECHANISM OF ACTION (Fig 10.3.11)

- Sodium nitroprusside cause activation of guanylyl cyclase, either via release of nitric oxide or by direct stimulation of the enzymein the vascular smooth muscle in both arteries and veins.
- The result is increased intracellular cGMP, which relaxes vascular smooth muscle, thus venodilatation leads to decreased preload and arteriolar dilatation leads to decreased afterload

(Fig 10.3.11)

USES

Congestive heart failure

DOSE AND ROUTE OF ADMINISTRATION

Dose is i.v infusion at 0.5 g/kg/min and may be increased up to 10 g/kg/min.

ADVERSE EFFECTS

- Metabolic acidosis, arrhythmias, excessive hypotension.

- Accumulation of cyanide may lead to cyanide poisoning (as nitroprusside is a complex of iron, cyanide groups, and a nitroso moiety)

Treatment

- Administration of sodium thiosulfate as a sulfur donor facilitates metabolism of cyanide.

- Hydroxocobalamin combines with cyanide to form the nontoxic cyanocobalamin.

- Both have been advocated for prophylaxis or treatment of cyanide poisoning during nitroprusside infusion.

DRUG INTERACTION

Increased systolic BP and decreased antihypertesive effect if taken concurrently with ergot alkaloids.

CONTRAINDICATION

Contraindicated with allergy to nitrates, severe anemia, head trauma, cerebral hemorrhage, hypertrophic cardiomyopathy, narrow-angle glaucoma and postural hypotension.

Nursing Implication

- Monitor constantly to titrate (either increase or decrease the dose) IV infusion rate to BP response.
- Relieve adverse effects by slowing IV rate or by stopping drug; minimize them by keeping patient supine.
- Notify physician immediately if BP begins to rise after drug infusion rate is decreased or infusion is discontinued.

- Monitor fluid Input & urine output

- Lab tests: Monitor blood thiocyanate level in patients receiving prolonged treatment or in patients with severe kidney dysfunction (levels usually are not allowed to exceed 10 mg/dL). Determine plasma cyanogen level following 1 or 2 d of therapy in patients with impaired liver function.

BETA ADRENOCEPTOR BLOCKERS or β BLOCKERS

- Propranolol (Non selective β blocker)

- Metoprolol
- Atenolol
- Bisoprolol

} Selective β_1 blocker

MESSAGE TO STUDENTS: Formula to remember the drugs used as β blockers or β receptor antagonist is "**P.MAB",** you can remember as **"P**lease **M**arry **A B**lind**",** which becomes **P**ropranolol , **M**etoprolol, **A**tenolol and **B**isoprolol. Here the names of all the drugs ends with common word **"olol",** you have to remember **Propran, Metopr, Aten** and **Biso**, which becomes **Propran**-olol , **Metopr**-olol**, Aten**-olol and **Biso**-prolol

MECHANISM OF ACTION (Fig. 10.5.9)

Sympathetic stimulation leads to increases apoptosis (cell death), down-regulation (decrease) in the concentration and sensitivity of β receptors and also increases mitogenic activity leading to cardiac remodeling.

β blockers blocks β receptors and brings following effects

- Decrease the effects of catecholamines (including apoptosis)
- Cause up-regulation and also increased sensitivity of β receptors
- Reduces remodeling through inhibition of the mitogenic activity of catecholamines.

(Fig. 10.5.9)

Fig.

Note: Sympathetic support is very much needed during heart failure, β blockers blocks may increase the complication. Hence it should be used with proper assessment of the condition starting with lowest dose and increased based on the response.

USES

Congestive heart failure

DOSE AND ROUTE OF ADMINISTRATION

Propranolol Oral: 10, 20, 40, 60, 80, 90 mg tablets; 4, 8, 80 mg/mL solutions, Oral sustained release: 60, 80, 120, 160 mg capsules and Parenteral: 1 mg/mL for injection

Metoprolol Oral: 50, 100 mg tablets, Oral sustained-release: 25, 50, 100, 200 mg tablets and Parenteral: 1 mg/mL for injection.

Atenolol Oral: 25, 50, 100 mg tablets and Parenteral: 0.5 mg/mL for IV injection

Bisoprolol Oral: 5, 10 mg tablets

ADVERSE EFFECTS

- Bradycardia caused by β blockers may cause life-threatening bradyarrhythmias in patients with partial or complete AV conduction defects.
- Fatigue, sleep disturbances (including insomnia and nightmares), and depression.
- Sudden or abrupt withdraw of β blockers may lead to rebound hypertension

DRUG INTERACTION

- **Cimetidine + β -blockers:** Decreased metabolism of β -blockers that are cleared primarily by the liver
- Aluminum salts, cholestyramine, and colestipol may decrease absorption of b blockers.

CONTRAINDICATION

Second or Third Degree Heart Block

Nursing Implication

- Obtain drug history
- Always check blood pressure before starting antihypertensive drug for the first time, if BP is below 90 systolic or 60 beats per minute (BPM) hold the drug and notify doctor.
- When patient are taking beta blockers, it is also very important to monitor the changes in lab values such as (protien, BUN and creatinine) which can indicate nephrotic syndrome.

- Advice patient **not stop taking drug suddenly**. Doing so may cause tachycardia, dysrythmias, elevated BP, angina and myocardial infarction..
- If patient is on extended release forms of the drug, advice not to be crushed and taken.

CHAPTER 10.6

ANTI-ARRHYTHMICS

Arrhythmia

Loss of cardiac rhythm where the heart rate either will be less than the normal or more than the normal due to abnormal cardiac electrical activity in the site of origin of the impulse, its rate or regularity, or in its conduction.

Physiology of Normal Cardiac Rhythm

- The electrical impulse first originates at regular intervals in the sinoatrial node (SA node), normally at a frequency of 60–100 beats per minute (Average 72 beats/min).
- This impulse generated passes rapidly through the atria and enters the atrioventricular node (AV node). The conduction through the AV node is slow which requires about 0.15 s. (The cause for this delay is to provide time for atrial contraction in order to propel blood into the ventricles.)
- Impulse from AV node then propagates over the His-Purkinje system and finally spreads to all parts of the ventricles.
- Ventricular activation is complete in less than 0.1 s, this is why, contraction of all of the ventricular muscle is synchronous and hemodynamically effective at regular intervals.

  So, any abnormality in the above said rhythm leads to arrhythmia.

Action potential: **(Fig. 10.6.1)**

Phase 0 (Rapid depolarization): In this phase, there will be activation of fast sodium channels leading to influx of sodium into the cell and **Rapid depolarization**. The action potential which was at -85mV suddenly shoots up to +30mV above zero.

Phase 1: (Early/Partial or Rapid repolarization) In this phase, there will be closure of fast sodium channel and potassium channel opens leading to Early/Partial or Rapid repolarization. The membrane potential drops to 0mV.

Phase 2 (Plateau phase): In this phase voltage sensitive Ca^{2+} channel opens leading Ca^{2+} entry into the cell which balances the slow outward K^{+} current (depolarization=repolarization) leading to plateau phase.

Phase 3 (Rapid Repolarization): In this phase, there will be closure of Ca^{2+} channel and opening of K^{+} channel which leads to pumping of K^{+} out of the cell. The membrane potential drops to -80mV.

Note: From the period of phase 0 to phase 3, there was entry of Na+ (with Ca2+) from outside in to the cell and loss of K+ from the cell to outside. But, the ionic balance will be restored by Na^{+} / K^{+} ATP ase

Phase 4 (Diastolic Depolarization): Here the membrane potential will be maintained around -90mV due to outward K^{+} leak current and by the action of Na^{+} / Ca^{2+} exchanger.

(Fig. 10.6.1)

Refractory period (Fig. 10.6.2)

Once the cardiac cell gets depolarized it will not respond to second stimulus (refractory), hence it is termed as refractory period. It is of three types as follows

Absolute Refractory Period (ARP)

From Phase 0 to mid of phase is Absolute Refractory Period (ARP) where the cell will not absolutely respond to any stimulus.

Relative Refractory Period (RRP)

As repolarization continues from mid of phase 3 towards phase 4, the cell can respond to strong second stimulus and hence it is termed as Relative Refractory Period (RRP)

Effective Refractory Period (ERP)

The sum of Absolute Refractory Period (ARP) and Relative Refractory Period (RRP) is Effective Refractory Period (ERP).

(Fig. 10.6.2)

Etiology of arrhythmia

Cardiac ischemia, Cardiac tissue hypoxia, metabolic acidosis or alkalosis, electrolyte imbalance (especially $K^{+,}$ hyper or hypokalemia), drug induced (eg, digitalis or any other antiarrhythmic drugs)

Pathophysiology of arrhythmia (Fig. 10.6.3)

The pathophysiology of arrhythmia may be due to disturbances of impulse formation or disturbances of impulse conduction.

I. Disturbances of impulse formation

- **Defect at SA node**

The impulse may be formed in SA node at a faster rate (upto 350 beats / min) called as tachy arrhythmia or may be slow (below 60 beat / min) called as brady arrhythmia.

- **Afterdepolarizations**

Interruption at phase 3 or Phase 4 of action potential as follows

1. **Early afterdepolarizations (EADs):**

Interruption of impulse at phase 3

2. **Delayed afterdepolarizations (DADs):**

Interruption of impulse at phase 4

(Fig. 10.6.3)

A. Normal action potential B. Early afterdepolarizations (EADs) C. Delayed afterdepolarizations (DADs)

II. Disturbances of Impulse Conduction

Heart block and reentry phenomenon are common disturbances of impulse conduction in heart.

Heart block: atrioventricular nodal block or bundle branch block leads to missing of beats.

Reentry phenomenon (also known as "circus movement"): Here one impulse reenters and excites areas of the heart more than once. **(Fig. 10.6.4)**

(Fig. 10.6.4)

Treatment of arrhythmias

Treatment of bradyarrhythmia

- Discontinue any medications that has slow down the heart rate
- Intravenous (IV) atropine: this medication may be used to temporarily increase heart rate as atropine blocks M_2 receptor in SA node of heart preventing the action of acetylcholine.
- Artificial pacemaker: this device may be either temporarily or permanently implanted under the skin in the chest wall. Whenever the heart rate drops too low, the pacemaker takes over the job of providing the electrical impulses needed to establish and maintain a normal heart rhythm.

Treatment of tachyarrhythmias

Here antiarrhythmics drugs are particularly helpful to bring back the abnormal rhythm towards normal rhythm. So, classification of antiarrhythmics usually the drugs used to treat tachyarrhythmia.

CLASSIFICATION OF ANTIARRHYTHMICS

CLASS I : Na^+ channel blockers are classified as Class 1A, Class 1B and Class 1C **Table. 10.6.1**

1A: Quinidine and Procainamide

1B: Lignocaine and Mexiletine

1C: Propafenone

- **CLASS II :** β blocker such as Propranolol, Esmolol and Sotalol
- **CLASS III :** K^+ channel blocker such as Amiodarone , Bretylium and Dofetilide
- **CLASS IV:** Ca^{2+} channel blocker such as **Phenylalkylamine : V**erapamil **and Benzothiazepine : D**iltiazem
- **Drug for Paroxysmal Supraventricular Tachycardia (PSVT):**

Adenosine

CLASS I
Na^+ CHANNEL BLOCKERS

DRUGS USED

1A: Quinidine and Procainamide **Table. 10.6.2 & Fig 10.6.5a**

1B: Lignocaine and Mexiletine **Table. 10.6.3 & Fig. 10.6.5b**

1C: Propafenone **Table. 10.6.4 & Fig 10.6.5c**

MESSAGE TO STUDENTS: Formula to remember the drug used as **CLASS I** antiarrhythmics is **"QP.LM.P",** you can remember as **"Q**uestion **P**aper **L**eaked **M**oney **P**lan**".** So **"QP"** becomes **Qui-ni-dine** and **Pro-cai-na-mide** under **Class IA**. **"LP"** becomes **Ligno-caine** and **Mexi-letine** under **Class IB** and **Pro-pa-fe-none** under **Class IC.**

MECHNANISM OF ACTION

All class I antiarrhythmics blocks Na^+ channels in cardiac cell. These drugs decrease phase 0 deporalization ans prolong repolarization.

Table. 10.6.1

DRUG CLASS	SPECIFIC MECHANISM OF ACTION	USES
Class IA	Shows intermediate Na^+ channel blocking and dissociation property which falls between Class IB and Class IC and prolong the Action Potential Duration (APD) (See Class IB and Class IC and again compare to Class IA)	Ventricular tachyarrhythmia
Class IB	Blocks Na^+ channel rapidly and also dissociate form Na^+ channel rapidly and no significant effects on the Action Potential Duration (APD)	Ventricular extrasystole due to myocardial infarction (MI)
Class IC	Blocks Na^+ channel slowly and also dissociate form Na^+ channel slowly and has minimal effects on the Action Potential Duration (APD)	Atrial flutter

Table. 10.6.2

DOSE AND ROUTE OF ADMINISTRATION	ADVERSE EFFECTS	DRUG INTERACTION	CONTRAINDICATION
Class IA **Quinidine** Oral: 200-400 mg three times a day or 5-8mg/kg i.v infusion at the rate of 0.3mg/kg/min.	Overdose leads to chinchonism which leads to nausea, tinnitus, headache, blurred vision etc	Quinidine inhibit cytochrome P450 enzymes and can increase plasma level of cholinesterase inhibitors	AV block, CHF, Hypotension and myasthenia gravis
Class IA **Procainamide** Oral 50mg/kg 6th hourly or i.v infusion of 1-1.5 mg/kg/min followed by maintainance dose of 1.5-5mg/kg/min	Cardiotoxic effects are similar to those of quinidine. New arrhythmias may be precipitated.	H2 blockers compete with procainamide for renal tubular secretion	AV block, CHF and Hypotension

Nursing implication

- Obtain drug history
- Always check blood pressure before starting antihypertensive drug for the first time, if BP is below 90 systolic or 60 beats per minute (BPM) hold the drug and notify doctor.

Quinidine

- Watch for signs and symptom of cinchonism (blurred vision, tinnitus, headache, psychosis); cramping and nausea and inform doctor, if any.

Procainamide

- Watch for Lupus like syndrome

Table. 10.6.3

DOSE AND ROUTE OF ADMINISTRATION	ADVERSE EFFECTS	DRUG INTERACTION	CONTRAINDICATION
Class IB **Lignocaine**			
Class IB **Mexiletine**			

Nursing implication

Table. 10.6.4

Class IC **Propafenone**			

Nursing implication

CLASS II
β BLOCKER

DRUGS USED

- Propranolol
- Esmolol
- Sotalol

MESSAGE TO STUDENTS: Formula to remember the drug used as **CLASS II** antiarrhythmics is **"PES",** you can remember as **"Please Escape suddenly"**, which becomes **Propranolol, Esmolol** and **Sotalol.** Here the names of all the drugs ends with common word **lol,** you have to remember **Proprana, Esmo and Sota,** which becomes **Proprana**-lol, **Esmo**-lol and **Sota**-lol.

MECHNANISM OF ACTION

Heart: Stimulation of β_1 receptors on SA node of the heart will increase heart rate and force of contraction.

So, β blockers blocks β_1 receptors on SA node of the heart and hence will decrease cardiac contractility (negative inotropic effect) and heart rate (negative chronotropic effect) **(Fig. 10.3.6)**

(Fig. 10.3.6)

USES

DOSE AND ROUTE OF ADMINISTRATION

- Propranolol Oral: 10, 20, 40, 60, 80, 90 mg tablets; 4, 8, 80 mg/mL solutions, Oral sustained release: 60, 80, 120, 160 mg capsules and Parenteral: 1 mg/mL for injection
- Bradycardia caused by β blockers may cause life-threatening bradyarrhythmias in patients with partial or complete AV conduction defects.
- Fatigue, sleep disturbances (including insomnia and nightmares), and depression.
- Sudden or abrupt withdraw of β blockers may lead to rebound hypertension
- Non selective β blocker like propranolol can worsen asthma by blocking β_2 in bronchial smooth muscle causein bronchoconstriction.

DRUG INTERACTION

- **Cimetidine + β -blockers:** Decreased metabolism of β -blockers that are cleared primarily by the liver
- Aluminum salts, cholestyramine, and colestipol may decrease absorption of b blockers.

CONTRAINDICATION

- Second or Third Degree Heart Block
- Bronchial asthma is a contraindication for Non selective β blockers (E.g. Propranolol)

Nursing implication

- Obtain drug history
- Always check blood pressure before starting antihypertensive drug for the first time, if BP is below 90 systolic or 60 beats per minute (BPM) hold the drug and notify doctor.
- When patient are taking beta blockers, it is also very important to monitor the changes in lab values such as (protien, BUN and creatinine) which can indicate nephrotic syndrome.
- Advice patient NOT STOP TAKING DRUG SUDDENLY. Doing so may cause tachycardia, dysrythmias, elevated BP, angina and MI.
- If patient is on extended release forms of the drug, advice not to be crushed and taken.

CLASS III
K^+ CHANNEL BLOCKER

DRUGS USED

- **A**miodarone
- **B**retylium
- **I**butilide
- **D**ofetilide

MESSAGE TO STUDENTS: Formula to remember the drug used as **CLASS III** antiarrhythmics is **"ABID",** you can remember as **"A**rrive **B**efore **I**ndependence **D**ay**",** which becomes **Amiodarone, Bretylium** and **Dofetilide.** Split the word of first two drugs and remember as **Ami-oda-rone** and **Brety-lium.**

The names of the last two drugs ends with a common word **"tilide",** you have to remember **Ibu** and **Dofe,** which become **Ibu-**tilide and **Dofe-**tilide.

MECHNANISM OF ACTION

These drugs predominantly blocks K^+ channels in cardiac smooth muscle and cause prolongation of the Action Potential Duration (APD) . **(Fig. 10.6.6)**

(Fig. 10.6.6)

Additional action

It also blocks Na^+ channels and β receptors

USES

To prevent recurrent ventricular tachycardia.

DOSE AND ROUTE OF ADMINISTRATION

- Amiodarone : A total loading dose of 10 g is usually achieved with 0.8–1.2 g daily doses. The maintenance dose is 200–400 mg daily.

- **Bretylium :** Intravenous bolus of 5 mg/kg over a 10-minute period. If needed repeat after 30 minutes. Maintainance dose will be a bolus of 5 mg/kg 4-6th hourly or constant infusion of 0.5–2 mg/min.

- **I**butilide: Parenteral: 0.1 g/mL solution for i.v infusion

- Dofetilide : Oral: 125, 250, 500 µg capsules

ADVERSE EFFECTS

Bradycardia and heart block in patients with preexisting sinus or atrioventricular node disease.

DRUG INTERACTION

Potassium channel openers like nicorandil may decrease the effect of potassium channel blockers.

Other potassium channel blockers like sulfonylurea may increase the effect of potassium channel blockers used in arrhythmia.

CONTRAINDICATION

Thyroid dysfunction, heart block, or sinoatrial node dysfunction

Nursing implication

- Peripheral i.v **A**miodarone concentration should not exceed 2mg/ml
- Oral administration / GI symptoms
- There are chances of lethal interstial pneumonitis in higher dose, be cautious about that.
- By weight amiodarone has 37% iodine, hence thyroid dysfunction may occur, verify with the lab report.

CLASS IV
Ca^{2+} CHANNEL BLOCKER

DRUGS USED

- **Phenylalkylamine : V**erapamil

- **Benzothiazepine : D**iltiazem

MESSAGE TO STUDENTS: Formula to remember the drug used as calcium channel blockers is "**VD",** you can remember as **"V**ictory **D**ay**".** Under **Phenylalkylamines** remember the drug **"V"** by splitting the word as "**Vera-pa-mil"** and under **benzothiazepine,** remember the drug **"D"** by splitting the word as **"Dil-tia-zem".**

MECHNANISM OF ACTION

Ca^{2+} channel blocker blocks calcium channel (L-type) and slows conduction in regions where the action potential upstroke is calcium dependent, eg, the sinoatrial and atrioventricular nodes **(Fig. 10.6.7)**

(Fig. 10.6.7)

USES

To suppress both early and delayed afterdepolarizations and also in supraventricular arrhythmias, including rate control in atrial fibrillation.

DOSE AND ROUTE OF ADMINISTRATION

Verapamil: Initial i.v. bolus of 5 mg over 2–5 minutes and if needed a second dose of 5mg after few minutes. Thereafter, doses of 5–10 mg every 4–6^{th} hourly, or a constant infusion of 0.4 g/kg/min.

Oral dosages 120 to 640 mg daily, divided into three or four doses.

Diltiazem Oral: 30, 60, 90 or 120 mg tablets, Oral sustained-release 60, 90, 120, 180, 240, 300, 360, 420 mg capsules and Parenteral: 5 mg/mL for injection can be administered based on the condition.

ADVERSE EFFECTS

- Dizziness or light-headedness
- Peripheral edema & Ankle swelling
- Headache
- Flushing or heat sensation
- Transient hypotension
- Nausea
- Constipation
- Bradycardia
- Rash

DRUG INTERACTION

- Verapamil and diltiazem reduce the elimination and increase the blood levels of carbamazepine (antiepileptics)and simvastatin (hypolipidemics). This can lead to toxicity from these drugs.

- Verapamil and diltiazem raise plasma digoxin levels which may lead to digoxin toxicity.

CONTRAINDICATION

- Patients with preexistent bradycardia, conduction defects, or heart failure caused by systolic dysfunction should not be given CCBs, especially the cardiac selective, non-dihydropyridines CCBs like Verapamil and diltiazem.

- Non-dihydropyridines like Verapamil and diltiazem, should not be administered to patients being treated with a beta-blocker because beta-blockers also depress cardiac electrical and mechanical activity and therefore the addition of a CCB augments the effects of beta-blockade.

Nursing Implication

- Obtain drug history
- Always check blood pressure before starting antihypertensive drug for the first time, if BP is below 90 systolic or 60 beats per minute (BPM) hold the drug and notify doctor.
- Avoidance patient to grapefruit juice during the therapy with CCBs as it may affect metabolism.
- Caution the patient that sudden withdrawal of CCBs may exacerbate angina.

DRUG FOR PAROXYSMAL SUPRA VENTRICULAR TACHYCARDIA (PSVT)

Adenosine is a nucleoside that occurs naturally throughout the body.

DRUGS USED

Adenosine

MECHNANISM OF ACTION

It acts on adenosine receptors on cell surface of AV node and terminates reentrant circuit through AV node and restores normal sinus rhythm

USES

It is the drug of choice in Paroxysmal Supraventricular Tachycardia (PSVT)

DOSE AND ROUTE OF ADMINISTRATION

i.v Bolus dose of 6 mg followed, if necessary, by a dose of 12 mg.

ADVERSE EFFECTS

Shortness of breath or chest burning, atrioventricular block and Atrial fibrillation

Less common toxicities include headache, hypotension, nausea, and paresthesias.

DRUG INTERACTION

- Carbamazepine with adenosine might cause the severe bradycardia.
- Methylxanthines block the affects of adenosine.

CONTRAINDICATION

- Second- or third-degree heart block (without a pacemaker)
- Sick sinus syndrome (without a pacemaker)
- Long QT syndrome
- Severe hypotension
- Decompensated heart failure

Nursing implication

- Caution patient to change positions slowly to minimize orthostatic hypotension.
- Be alert that doses of adenosine >12 mg decrease BP by decreasing peripheral vascular resistance and may worsen the condition.
- Instruct patient to report facial flushing, shortness of breath, or dizziness.

General Nursing implication when administering antiarrhythmic drugs

- Check BP and apical pulse before administration of drugs
- Monitor vital signs
- Monitor ECG
- Monitor kidney and liver function and correlate with lab report
- Monitor serum drug levels
- Monitor electrolyte levels
- Teach patient about side effects of the drugs
- Advice patient not stop treatment abruptly
- Advice patient to take drugs as prescribed by the doctor
- Advice patient to avoid caffeine
- Advice patient to avoid alcohol

CHAPTER 10.7

HYPOLIPIDEMICS

INTRODUCTION

Lipoproteins are lipids complexed with proteins which circulate in blood. These are as follows

- Low density lipoproteins (LDL)
- High density lipoproteins (HDL)
- Very low density lipoproteins (HDL)
- Chylomicrons

Their normal level in blood leads to proper health (Table). Dyslipidemias, including hyperlipidemia (hypercholesterolemia) and low levels of highdensity- lipoprotein cholesterol (HDL-C), are major causes of increased atherogenesis, coronary heart disease (CHD), ischemic cerebrovascular disease or peripheral vascular disease.

Table.10.7.1 National Cholesterol Education Program: Adult Treatment Guidelines (2001).

	Desirable **mg/dL (mmol/L)**	**Borderline to High** **mg/dL (mmol/L)**	**High** **mg/dL (mmol/L)**
Total cholesterol	< 200 (5.2)	200–392 (5.2–6.2)	> 240 (6.2)
LDL cholesterol	< 130 (3.4)	130–159 (3.4–4.1)	> 160 (4.1)
HDL cholesterol			> 60 (1.55)
Men	> 40 (1.04)		
Women	> 50 (1.30)		
Triglycerides	< 150 (1.7)	150–199 (1.7–2.3)	> 200 (2.3)

If there is abnormality of these lipoproteins level in blood found after a lab investigation, then it is called as abnormal lipid profile where there may be increase in any one of lipoprotein (Total cholesterol, LDL or Triglyceride) or any one of them may have been increased with or without decrease in HDL. Please note that HDL is a good cholesterol and its level should be always high in blood, but increase in Total cholesterol, LDL or Triglyceride leads to risk of developing atherogenesis, coronary heart disease (CHD), ischemic cerebrovascular disease or peripheral vascular disease.

Aim of the therapy should be

- Decrease the synthesis of cholesterol by using **HMG-CoA reductase inhibitors**
- Increase the activity of lipoprotein lipase by using **Fibric acid derivatives**
- Decrease VLDL secretion by using **Niacin (Nicotinic Acid) - vitamin B_3**
- Prevent the absorption of bile by using **Bile Acid-Binding Resins**
- Prevent the dietary absorption of cholesterol by using **Inhibitors of Intestinal Sterol Absorption**

CLASSIFICATION OF HYPOLIPIDEMICS

1. **HMG-CoA reductase inhibitors**

- Rosuvastatin
- Fluvastatin
- Lovastatin
- Atorvastatin
- Pravastatin
- Simvastatin

2. **Fibric acid derivatives**

- Gemfibrozil
- Fenofibrate
- Bezafibrate

3. **Drug Decreasing VLDL secretion**

Niacin (Nicotinic Acid) - vitamin B_3

4. **Bile Acid-Binding Resins**

- Colestipol
- Colesevelam
- Cholestyramine

5. **Inhibitors of Intestinal Sterol Absorption**

- Ezetimibe

HMG-CoA REDUCTASE INHIBITORS

DRUGS USED

- Rosuvastatin
- Fluvastatin

- Lovastatin
- Atorvastatin
- Pravastatin
- Simvastatin

MESSAGE TO STUDENTS : Formula to remember HMG-CoA reductase inhibitors is "**R.FLAPS**", remember as **R.FLAPS** only, which becomes **Rosuvastatin, Fluvastatin, Lovastatin, Atorvastatin, Pravastatin and Simvastatin.** Here the names of all the drugs ends with common word **"statin",** you have to remember **Rosuva, Fluva, Lova, Atorva, Prava** and **Simva** , which becomes **Rosuva**-statin, **Fluva**-statin, **Lova**-statin, **Atorva**-statin, **Prava**-statin and **Simva**-statin.

If you still can't remember any drugs, then you can just write as **"Statins"** are **HMG-CoA reductase inhibitors.**

MECHANISM OF ACTION

- HMG-CoA reductase enzyme involves in an important step in cholesterol synthesis.
- HMG-CoA reductase inhibitors (statins) inhibit the enzyme HMG-CoA reductase and decrease the synthesis of cholesterol. **(Fig. 10.7.1)**

(Fig. 10.7.1)

USES

HMG-CoA reductase inhibitors alone or with resins, niacin, or ezetimibe in reducing levels of LDL in Dyslipidemias, including hyperlipidemia (hypercholesterolemia)

DOSE AND ROUTE OF ADMINISTRATION

- Rosuvastatin : oral 10–40 mg/d
- Fluvastatin: oral 10–80 mg daily.
- Lovastatin: oral 10 mg - 80 mg
- Atorvastatin: oral 10–80 mg/d
- Pravastatin: oral 80 mg /d
- Simvastatin: oral 5–80 mg daily

ADVERSE EFFECTS

- Elevations of serum aminotransferase activity
- Rhabdomyolysis
- Myopathy

DRUG INTERACTION

- Concomitant use of HMG-CoA reductase inhibitors with amiodarone or verapamil also causes an increased risk of myopathy.
- Phenytoin, griseofulvin, barbiturates, rifampin, and thiazolidinediones increase the level of liver enzymes and decrease the plasma level HMG-CoA reductase inhibitors.

CONTRAINDICATION

Pregnancy and lactation, Liver Disease with Liver Enzymes and known allergy to the drug.

Nursing implication

- Obtain history of drug allergy
- Patients taking statins should be monitored for creatine kinase along with their blood lipids and liver enzymes to reduce the risk of statin-induced rhabdomyolysis.
- It better to give the drug at bed time to get maximum therapeutic benefit

FIBRIC ACID DERIVATIVES (FIBRATES)

DRUGS USED

- Gemfibrozil
- Fenofibrate
- Bezafibrate

MESSAGE TO STUDENTS : Formula to remember Fibric Acid Derivatives is **GFB**, you can remember as "**G**irl **F**riend **B**eautiful", which becomes **Gemfibrozil , Fenofibrate and Bezafibrate.** The name of the first drug can be remembered by splitting it as **"Gem-fibro-zil".** The name of the second and third drug ends with a common word **"fibrate",** you have to remember **Feno** and **Benza**, which becomes **Feno**-fibrate and **Beza**-fibrate.

MECHANISM OF ACTION

- Fibrates acts on nuclear transcription receptor, peroxisome proliferator-activated receptor-alpha (PPAR- α) and enhance the activity of *lipoprotein lipase*.
- *lipoprotein lipase* increase lipo-lysis of lipoprotein triglyceride **(Fig. 10.7.2)**

(Fig. 10.7.2)

USES

In hypertriglyceridemias (increased triglycerides)

DOSE AND ROUTE OF ADMINISTRATION

Gemfibrozil : oral 600 mg orally once or twice daily

Fenofibrate : oral one to three 54 mg tablets (or a single 160 mg tablet)

Bezafibrate : 200mg once or twice daily

ADVERSE EFFECTS

- Rashes, gastrointestinal symptoms, myopathy, arrhythmias, hypokalemia, and high blood levels of aminotransferases or alkaline phosphatase.
- Rhabdomyolysis may occur rarely.

DRUG INTERACTION

- Absorption of fibrates is improved when they are taken with food.
- Fibrates potentiate the action of warfarin and may result in bleeding
- Risk of myopathy increases when fibrates are given with HMG-CoA reductase inhibitors

CONTRAINDICATION

Known hypersensitivity to the drug, hepatic , gallbladder or renal dysfunction

Nursing implication

- Periodically monitor lipid levels, liver functions, and Complete Blood Count with differential.
- Assess for muscle pain, tenderness, or weakness and, if present , inform the treating doctor

- Inform doctor i immediately if any of the following signs and symptoms develops: Unexplained muscle pain, tenderness, or weakness, especially with fever or malaise; yellowing of skin or eyes; nausea or loss of appetite; skin rash or hives.
- Inform physician regarding concurrent use of cholestyramine, oral anticoagulants, or cyclosporine.
- Advicenursing mother not to breast feed after taking this drug.

DRUG DECREASING VLDL SECRETION

DRUG USED

Niacin (Nicotinic acid) - Vitamin B_3

MECHANISM OF ACTION

- Niacin inhibits VLDL secretion, in turn decreasing production of Low Density Lipoprotein (LDL)
- Increase in clearance of Very Low Density Lipoproteins (VLDL) via the *Lipoprotein lipase* (LPL) pathway contributes to triglyceride reduction. **(Fig. 10.7.3)**

(Fig. 10.7.3)

USES

- In combination with a Bile acid binding resin or HMG-CoA reductase inhibitor, niacin normalizes LDL level in most patients with heterozygous familial hypercholesterolemia and other forms of hypercholesterolemia.
- In combined hyperlipoproteinemia and in those with familial dysbetalipoproteinemia.
- In severe mixed lipemia with hypertriglyceridemias (increased triglycerides), it can be given with Bile acid binding resin or HMG-CoA reductase inhibitor

DOSE AND ROUTE OF ADMINISTRATION

Niacin: oral 100 mg as a starting dose for two or three times daily with meals. Dose can vary from 1.5-6gm depending on the conditions.

ADVERSE EFFECTS

Nausea, abdominal discomfort Pruritus, rashes, dry skin or mucous membranes and acanthosis nigricans.

Note: Niacin causes vasodilatation, flushing and a sense of warmth which is harmless

DRUG INTERACTION

- Niacin should not be taken at the same time as the antibiotic tetracycline because niacin interferes with the absorption of tetracycline.
- Niacin increase the effect of anticoagulants (blood thinners) leading to bleeding

CONTRAINDICATION

Severe peptic disease and Hepatic dysfunction

Nursing implication

- Nurse should warn patients to expect the flush and flush and explain that it is a harmless side effect.
- Monitor for visible sins of red tongue, excessive saliva secretion and infection of oral membranes, nausea, vomiting, diarrhea, confusion, if any, inform the doctor.
- Monitor diabetics parient for signs of hyperglycemia, glycosuria, ketonuria, and increased insulin because they may need increased requirements of insulin.
- Observe for signs and symptoms of jaundice, dark urine, light-colored stools, pruritus which indicate liver dysfunction and joint, or stomach pain; altered urine excretion pattern which indicate hyperuricemia and may predispose to gout.
- Advice patient to avoid alcohol, because alcohol and large doses of niacin cause increased flushing and sensation of warmth.
- Advice nursing mother not to breast feed while taking this drug.

BILE ACID-BINDING RESINS

DRUGS USED

- Colestipol
- Colesevelam
- Cholestyramine

MESSAGE TO STUDENTS : Formula to remember bile acid-binding resins is **C^3 ,** you can remember as **"C qube",** which becomes **Colestipol, Colesevelam** and **Cholestyramine.** Here the names of the first two drugs starts with the common word **"Cole"** and the name of the third drug starts with **"Chole",** you have to remember **sti-pol, seve-lam** and **styra-mine.** Now write as **Cole, Cole** and **Chole** and add **sti-pol, seve-lam** and **styra-mine** which becomes **Cole-stipol, Cole-sevelam** and **Chole-styramine.**

MECHANISM OF ACTION

- Bile acids that are secreted to intestine through bile duct are needed for intestinal absorption of cholesterol.
- The bile acid binding resins are not absorbed when taken orally and they bind to bile acids in the intestine. So, when bile acids are not absorbed, even the cholesterol is not absorbed leading to decreased level of plasma cholesterol and LDL. **(Fig. 10.7.4)**

(Fig. 10.7.4)

USES

In primary hypercholesterolemia

DOSE AND ROUTE OF ADMINISTRATION

Colestipol: oral 1 g tablets swallowed as a whole **(**maximum dose is 16 g daily**)**

Colesevelam:oral 625 mg tablets.(maximum dose is six tablets daily)

Cholestyramine: 4 g (1 packet) 1 to 6 times daily depending on circumstances.

ADVERSE EFFECTS

- Constipation and bloating
- Heartburn and diarrhea rarely

DRUG INTERACTION

- Bile acid-binding resins + vitamin K or folic acid: Malabsorption of vitamin K or folic acid
- Bile acid-binding resins also inhibit absorption of digitalis glycosides, thiazides, warfarin, tetracycline, thyroxine, iron salts, pravastatin, fluvastatin, folic acid, phenylbutazone, aspirin, and ascorbic acid.

CONTRAINDICATION

Diverticulitis

Nursing implication

Prothrombin time should be measured frequently in patients who are taking resins and anticoagulants.

Any additional medication (except niacin) should be given 1 hour before or at least 2 hours after the resin to ensure adequate absorption.

INHIBITORS OF INTESTINAL STEROL ABSORPTION

DRUG USED

- Ezetimibe

MECHANISM OF ACTION

- Ezetimibe is a selective inhibitor of intestinal absorption of cholesterol and phytosterols.
- It inhibits reabsorption of dietary cholesterol.
- It is also effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in the bile.

USES

To reduce LDL cholesterol

DOSE AND ROUTE OF ADMINISTRATION

Ezetimibe **:** Single daily dose of 10 mg orally

ADVERSE EFFECTS

- Diarrhea
- Cough
- Myalgia
- Arthralgia
- Fatigue
- Increased liver transaminases

DRUG INTERACTION

Cholestyramine and colestipol may bind to ezetimibe and prevent absorption

CONTRAINDICATION

Concomitant use with HMG-CoA reductase inhibitors in patients with active liver disease or unexplained persistent elevations in serum transaminases

Nursing implication

- Obtain drug history
- If a patient is taking a bile acid sequestrant (such as cholestyramine, colestipol) advice to take ezetimibe at least 2 hours before or 4 hours after taking the bile acid sequestrant.

CHAPTER 10.8
VOLUME EXPANDERS

OR

PLASMA VOLUME EXPANDERS

A volume expander or plasma volume expanders are a type of intravenous therapy that is aimed to provide volume for the circulatory system.

It can also be used for fluid replacement.

Need for volume or plasma expansion

Plasma volume expanders are used for the treatment of circulatory shock. They restore vascular volume, stabilising circulatory haemodynamics and maintaining tissue perfusion.

How do plasma volume expanders work?

Plasma volume expanders increase the oncotic pressure in the intravascular space. Water moves from the interstitial spaces into the intravascular space, increasing the circulating blood volume. This increased volume leads to an increase in central venous pressure, cardiac output, stroke volume, blood pressure, urinary output and capillary perfusion, and a decrease in heart rate, peripheral resistance and blood viscosity.

Types of plasma volume expanders

Crystalloids or colloids, or a mixture of both

- Crystalloids are aqueous solutions of mineral salts or other water-soluble molecules. **Table 10.8.1**

- Colloids are larger insoluble molecules, such as gelatin and even blood itself is a colloid. **Table 10.8.2**

Table 10.8.1

CRYSTALLOIDS	COMPOSITION	DOSE & ROUTE OF ADMINISTRATION	USES	SIDE / ADVERSE EFFECTS
Normal saline (NS)	0.91% w/v of NaCl, about 300 mOsm/L.[	i.v infusion as recommended by treating doctor	In patient who are in danger of developing dehydration or hypovolemic shock in hospital setting.	Febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation, and hypervolemia.
Ringer's solution (Lactated Ringer's solution)	28 mmol/L lactate, 4 mmol/L K+ and 1.5 mmol/L Ca2+.	i.v infusion as recommended by treating doctor	Used for large-volume fluid replacement in case of severe volume loss in hospital setting.	Allergic reactions or anaphylactoid symptoms such as localized or generalized urticaria and pruritus; periorbital, facial, and/or laryngeal edema; coughing, sneezing, and/or difficulty with breathing.
Glucose (dextrose) Types of glucose/dextrose 1. D5W	(5% dextrose in water)	i.v infusion as recommended by treating doctor	When patient is at risk for having low blood sugar or high sodium or useful in traumas when there's a shock related calorie burn in hospital setting.	Redness or pain at the injection site, fever, trouble breathing, swelling etc
2. D5NS	(5% dextrose in normal saline)	i.v infusion as recommended by treating doctor	Fluid and electrolyte	Reactions which may occur because of the

			replenishment and caloric supply in hospital setting	solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.

Table 10.8.2

COLLOIDS	COMPOSITION	DOSE & ROUTE OF ADMINISTRATION	USES	SIDE / ADVERSE EFFECTS
Hetastarch	Nonionic starch derivative	**Hypovolemia** 500-1000 mL (30-60 g) IV Not to exceed 1500 mL/day (20 mL/kg) **Leukapheresis** 250-700 mL Hespan to which citrate anticoagulant has been added	To prevent shock following severe blood loss caused by trauma, surgery, or other problem.	Anaphylactoid reactions: hypersensitivity, mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm and non-cardiogenic pulmonary edema.
Albumin	Albumin is a small a endogenous protein	• Infusion rate: 25% vials: 2-3 ml/minute maximum. • 5% solution: 5-10 ml/minute maximum. • Discard unused solution after 4 hours. • Dilute if necessary with D5W or NS. • Hypoproteinemia (Usual dose): 0.5- 1 gram/kg/dose q1-2	• To replace lost fluid and help restore blood volume in trauma, burns and surgery patients. • For subjects with hypoalbuminemia who are critically ill and/or are	Hypersensitivity or allergic reactions

		days as calculated to replace ongoing losses. • Maximum dose/day: 250 grams/48 hours.	bleeding actively,	
<u>Dextrans</u> • **Dextran 1** • **Dextran 40** • **Dextran 60** • **Dextran 70** (The number indicates molecular weights ranging)	Soluble, biodegradable and biocompatible biopolymers comprised by glucose units	**Adjunctive therapy in shock:** • Total dosage of 20 mL/kg IV in first 24 h. • The first 10 mL/kg should be infused rapidly, the remaining dose administered slowly. • Beyond 24 h, total daily dosage should not exceed 10 mL/kg. • Do not continue therapy for more than 5 d. **Hemodiluent in extracorporeal circulation:** • Generally 10---20 mL/kg are added to perfusion circuit. Do not exceed a total dosage of 20 mL/kg. **Prophylaxis therapy for Deep Vein Thrombosis:** • 500---1,000 mL IV on day of surgery, continue treatment at dose of 500 mL/d for an additional 2---3 d. • Thereafter, based on procedure and risk, 500 mL may be administered every second to third day for up to 2 wk.	•Replacement of blood loss •Plasma substitution •Thrombosis prophylaxis •Volume expansion •Rheological improvement	Febrile response, infection at the injection site, venous thrombosis or phlebitis extending from the injection site, extravasation, and hypervolemia

Nursing implication

- Obtain drug history
- Nurses trying to infuse of plasma expanders must be aware of the possible complications.
- Anaphylaxis reactions can occur with hetastarch, albumin or any of the dextran preparations.
- Especially dextran is produced by a bacterium, Leuconostoc mesenteroides, which contributes to its antigenicity.
- With albumin, anaphylactic reactions are more likely to occur with high doses, So repeat administer with low doses.
- With any product, the patient should be closely observed during the first few minutes of administration.
- Allergic reactions include urticaria, nasal congestion, wheezing, tightness of the chest, nausea and vomiting, periorbital oedema and hypotension, which can be mild or severe. Volume expander therapy should be stopped at the first sign of an allergic reaction and inform the treating doctor.
- Patients with a reduced flow of urine are particularly susceptible to tubular stasis and blocking, so it is essential to maintain hydration.
- Monitor fluid input and output as volume overload may worsen renal failure and lead to cardiovascular effects.
- Excessive administration of albumin, dextran or hetastarch can precipitate cardiac failure, pulmonary oedema and peripheral oedema of the lower extremities, hypertension or tachycardia. Concentrations in plasma protein fraction may cause a higher incidence of hypotension. Hence nurses need to monitor patient's haemodynamic state frequently.
- Bleeding is one of the problems with hetastarch therapy. Hetastarch affect total platelet count and hence haemodilution can exacerbate this. A prolonged bleeding time, partial thromboplastin time and prothrombin time can result as a temporary adverse effect.