UNIT 5 DRUGS ACTING ON BLOOD

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5.1 INTRODUCTION

Blood is a fluid connective tissue that transports oxygen, nutrients and growth factors to individual cells of the body. The main components of blood are cell (like RBCs, WBCs, platelets), proteins (like coagulation factors, amino acids, growth factors, factors of the complement system), monosaccharide (ribose, glucose), minerals (Na+, K+, Cl-, HCO3-), and water. A lot of drugs can have an effect of one or more of these components and can bring about a change in the physiological homeostasis. In this unit we will be discussing those drugs that are useful in the treatment of disorders of the haemopoietic system.

Objectives

After studying this unit, you should be able to:

- discuss about anaemia which occur due to decrease in number of red blood cells or haemoglobin content, amemias caused by blood loss, deficient erythropoiesis, excessive haemolysis, or combination of these changes;
- enumerate the conditions where plasma substitutes/expanders are used;
- about coagulants and anticoagulants. Enumerate their therapeutic uses; and
- discuss about the drugs used in the treatment of hyperlipidemias.

5.2 HAEMATINICS AND PLASMA EXPANDERS

5.2.1 Anaemia

Anaemia is the decrease in number of red blood cells or hemoglobin content caused by blood loss, deficient erythropoiesis, excessive hemolysis, or combination of these changes. Iron deficiency anaemia is probably the most common nutritional deficiency in the world. It is estimated that at least 500 million people are affected. Iron deficiency anaemia is much more common in developing countries, as people are consuming too little food or a limited variety of food.

Infants and young children have higher iron requirement. For the first six months of life, these requirements are met by iron store in the infant's body alone with supplementation from breast or formula milk. Iron requirement increases during adolescence because of growth, muscle development and, for girls, at the start of menstruation. Adult women have higher iron requirement because of menstrual losses. During pregnancy it is not necessary to have extra iron in the diet because absorption increases and menstruation stops. The fetus is likely to get enough iron even if its mother has low stores, but mother becomes anaemic.

Anaemia may be classified into different groups according to the pathophysiology.

1. Dietary deficiency anaemia, which is due to deficient supply of various factors e.g. iron, folic acid, vitamin B_{12}, vitamin C and pyridoxine which are essential for normal blood formation.

2. Anaemia due to blood loss e.g. in severe gastric blood loss (ulcers), protozoal or worm infestation.

3. Anaemia due to excessive destruction, of blood e.g. sickle cell anaemia and haemolytic anaemia.

4. Anaemia due bone narrow depression e.g. aplastic and hypoplastic anaemia.

5.2.2 Iron

The body iron is distributed mainly in two forms, one as haem in haemoglobin and cytochrome oxidase enzyme and other as iron bound to protein as storage compounds ferritin and hemosiderin, and as transport iron bound to transferrin. The total iron in human adult is approximately 3.5g.

After oral administration iron is absorbed in ferrous form. The conversion of ferric iron to ferrous iron is aided by hydrochloric acid. Only little amount of iron is lost by shedding of intestinal mucosal cells and trace amount is excreted in urine, sweat and bile.

After confirmation of iron deficiency iron therapy can be given by oral or parenteral route. Generally oral iron therapy is given unless the patient is

suffering from severe anaemia, malabsorption syndrome, gastrectomy or patient is showing adverse effects to oral iron therapy.

It is used in the treatment of nutritional iron deficiency anaemia, during pregnancy, lactation, to prevent iron deficiency in infants and children. In patients with malabsorption syndrome, patients who are taking Non-steroidal anti inflammatory drugs (NSAID's) for long period, patients with chronic inflammatory disease and in patients of gastrectomy.

Preparations of iron alone or in combination with vitamin B_{12}, folic acid are also available. Iron preparations also available in injection (parenteral) form as Iron dextran and Iron sorbitol citric acid complex.

5.2.3 Errythropoietin

It is produced primarily by the kidneys. In anaemia renal secretion of erythropoietin increases rapidly manifold. Erythropoietin levels are always detectable in plasma.

It stimulates proliferation, maturation and haemoglobin formation by committed erythroid progenitors.

Recombinant human erythropoietin is available. It is given by parenteral route (iv or sc).

It is **used** in the treatment of anaemia of chronic renal failure, in anaemia of patients with AIDS who are being treated with zidovudine and anaemia associated with cancer chemotherapy.

SAQ 1

a) The total iron in human adult is approximately _____.

b) In blood iron is bound to the protein _____.

c) _____ is the chelating agent used in iron overdose.

d) _____ stimulates proliferation, maturation and haemoglobin formation by committed erythroid progenitors.

5.2.4 Plasma Expanders

Plasma substitutes/expanders are high molecular weight substances, which when infused intravenously into blood stream retain fluid in the vascular compartment and exert osmotic pressure. They are used in conditions where blood plasma has been lost e.g. shock, burn cases, severe trauma and extensive tissue damage as a temporary measure till the blood can be arranged. These do not have O_2 carrying capacity. The clinically used plasma expanders are discussed here.

Human Albumin: It is obtained from heat treated pooled human plasma. It draws and holds additional fluid from tissues. It can be used irrespective of patient's blood group. It does not interfere with coagulation and there is no risk of sensitization.

Dextrans: It is the most commonly used plasma expander. It is polysaccharide isolated from beet sugar which is formed by the action of leuconstec mesenteroides. It is available in two forms depending upon the molecular weight. Dextran 70 (mol. Wt. 70,000) and dextran 40 (mol. Wt. 40,000). They are infused intravenously in the treatment of shock.

Degraded Gelatin Polymer – Polygeline: It is a polypeptide similar to albumin. It does not interfere with blood grouping and cross matching. It is a plasma substitute which corrects circulatory insufficiency due to plasma/blood volume deficiency.

Hydroxyethyl Starch: It is similar to glycogen, the starch molecule is substituted to a selected degree to achieve a distinct plasma retention and volume effect. It improves haemodynamics, macrocirculation, microcirculation, organ function, oxygen supply.

Polyvinylpyrrolidone (PVP): It is a synthetic, water soluble polymer of molecular weight approximately 40,000. It interferes with blood grouping and cross matching. It also binds certain drugs i.e. Insulin, penicillin etc. Because of these draw-backs, it is less commonly used.

Dextrose (5%) Solution

1. It is used in prevention of dehydration of all types, excessive tissue protein catabolism, depletion of liver glycogen and as a vehicle for IV administration of numerous drugs.
2. When oral intake of food and water is limited as in pre and postoperative patients or in the patients with severe hepatic or cardiac or GIT disease.
3. Correction of deficit of water as in case of inadequate intake and excessive losses in urine and perspiration.
4. In the treatment of ketosis in starvation, diarrhoea, vomiting or high fever.
5. In promotion of sodium excretion when there is excess sodium in the body due to excessive use of electrolyte solutions.
6. To provide adequate calories to the body.

Normal Saline

It is indicated in:

1. When alkalosis is present along with fluid loss.
2. In case of severe salt depletion when rapid electrolyte restoration is essential.
3. In the treatment of low salt syndrome which may occur in presence of heart failure, renal impairment, during surgery, etc. In these cases chloride loss frequently exceeds sodium loss.
4. In severe salt depletion resulting from excessive fluid loss due to sweating, vomiting, diarrhoea, etc.

Ringer Lactate

Ringer lactate (contain calcium chloride, potassium chloride, sodium chloride and sodium lactate) is **indicated** in:

1. For replacing the deficit of extra cellular fluid due to decreased water intake or increased secretion of water even in absence of marked acid base disturbance.
2. In case of burns, infections, fractures, peritoneal irrigation etc., for the restoration of normal extra cellular fluid balance during surgery.
3. In moderate metabolic acidosis which occurs in cases of mild renal insufficiency, infant diarrhoea, diabetic ketosis etc.
4. During or after giving anaesthesia, to correct metabolic acidosis which results from disturbed respiration.

SAQ 2

a) _____ are the most commonly used plasma expanders.

b) Plasma expanders _____ have O_2 carrying capacity.

c) Define anaemia.

5.3 COAGULANTS AND ANTICOAGULANTS

5.3.1 Introduction

Thrombogenesis is an abnormal state of haemostasis leading to the formation of arterial and venous thrombus, also known as white and red thrombus respectively. Haemostasis is the spontaneous arrest of bleeding from the damaged blood vessels.

Coagulation of blood comprises the formation of fibrin. There are thirteen factors (that are synthesized in the liver) which are involved in the coagulation of blood.

Review of Clotting Mechanism

Haemostasis: Haemostasis refers to the arrest of blood loss from a damaged blood vessel i.e. stoppage of bleeding. The mechanism is essential to maintain life. In case of any damage to a blood vessel, the haemostatic response must be:

- Quick.
- Controlled & localized to region of damage.

Three basic measures taken by the body to reduce and stop blood loss are:

i) Vascular spasm.
ii) Platelet plugs formation.
iii) Clotting or coagulation.

Clotting: Normally, blood remains liquid as long as it is flowing within intact smooth blood vessels. But on damage to the blood vessel and/or if blood is extracted from the blood vessel, there is conversion of liquid to gel state. This gel, on solidification gives a clot. The process of conversion of liquid to gel is termed as coagulation.

Clotting involves several factors called clotting factors. These include calcium, several inactive enzymes synthesized by hepatocytes and various molecules associated with platelets and/or released by the damaged tissue. The clotting factors are denoted by Roman numeral, denoting the order of their discovery (Table 5.1).

Table 5.1: Clotting factors

I. Fibrinogen.

II. Prothrombin.

III. Thromboplastin.

IV. Calcium.

V. Proaccelerin.

VI. Accelerin.

VII. Serum prothrombin conversion accelerator.

VIII. Antihaemophilic factor.

IX. Plasma thomboplastin component.

X. Stuart Prower factor.

XI. Plasma thromboplastin antecedent.

XII. Hageman factor.

XIII. Fibrin stabilizing factor.

Stages of Clotting

Formation of prothrombinase: It can be formed by extrinsic pathway and intrinsic pathway.

Extrinsic pathway: This pathway has fewer steps than the intrinsic pathway and occurs rapidly, within a matter of seconds if the trauma is severe. It is called the extrinsic pathway because a protein tissue factor, also called thromboplastin or coagulation factor III, enters into the blood stream from outside and initiates the formation of prothrombinase. Tissue factor is released from the surface of the damaged cells. It activates factor VII. Factor VII combines with factor X, activating it. Factor X in the presence of Ca^{2+} combines with factor V to give active enzyme prothrombinase.

Intrinsic pathway: This pathway is more complex and is much slower. It is so named as the activators are in direct contact with the blood in the intact blood vessels. No outside tissue damage is required. A rough vessel with exposed collagen is sufficient. Contact with collagen activates factor XII. This in turn

activates factor IX. Factor IX joins factor VIII and this gives active factor X. Factor X joins with calcium to bring about the formation of prothrombinase.

Once prothrombinase has been formed, the **common pathway** is followed. In stage 2, prothrombinase and calcium catalyze the conversion of prothrombin to thrombin. In stage 3, thrombin, in the presence of calcium converts soluble fibrinogen to insoluble fibrin threads.

5.3.2 Coagulants

These are the agents that promote coagulation and are mainly used in any haemorrhagic condition. They are classified as in Table 5.4.

Vitamin K: Vitamin K is a fat soluble vitamin found primarily in leafy green vegetables. Most of the vitamin k is synthesized by intestinal microorganisms and there is a risk of vitamin K deficiency in new born infants. Vitamin K is necessary for final stage of synthesis of coagulation factors (mainly factor II, VII, IX and X) in liver. The deficiency of vitamin K occurs due to liver disease, jaundice, malabsorption syndromes and chronic use of antimicrobial agents. Therapeutically, vitamin K is used in prophylaxis and treatment of deficiency of clotting factor due to dietary deficiency of vitamin K, chronic antimicrobial therapy, malabsorption syndrome, obstructive jaundice, liver diseases such as cirrhosis and hepatitis, in neonates to prevent or treat haemorrhagic disease of new born; to counteract the overdosing of oral anticoagulants.

The vitamin K analogus used clinically are Menapthone, Menadione, Phytomenadione. Other drugs used as coagulants are tranexamic acid and polidocanol.

5.3.3 Anticoagulants

These are the drugs used to reduce the coagulability of blood. The most important anticoagulants is heparin. The detail pharmacology is discussed here.

Heparin

Heparin is a heterogenous mixture of sulfated mucopolysaccharides and quick acting anticoagulant which shows efficacy both *in vitro* and *in vivo* and having a molecular weight from 4,000 to 40,000 depending upon the type of preparations. Its biological activity is dependent upon the plasma protease inhibitor antithrombin III, which inhibits clotting factor proteases by forming equimolar stable complexes with them.

It acts by activating plasma antithrombin III which rapidly inhibits activated coagulation factors IXa, Xa, XIa and XIIa, plasmin, kallikrein and thrombin, thus inhibiting conversion of fibrinogen to fibrin.

It is indicated in the prophylaxis and treatment of deep vein thrombosis in major surgery and pulmonary embolism, treatment of atrial fibrillation with embolisation, prophylaxis and treatment of peripheral arterial embolism.

Low Molecular Weight Heparins (LMWH)

These are prepared by enzymatic or chemical hydrolysis of conventional heparin, their molecular weight varies from 3,000 to 7,000.

It is indicated in prevention and treatment of deep vein thrombosis and pulmonary embolism in surgical patients, prevention of extracorporeal thrombosis during haemodialysis.

The clinically used low molecular weight heparins are enoxaparin, reviparin, dalteparin, nadroparin, ardeparin and tinzaparin etc.

Heparinoids

Ancrod is an enzyme obtained from Malayan pit viper venom. It produces heparin like effect by degrading fibrinogen into an unstable form of fibrin.

Danaparoid is isolated from porcine intestinal mucosa and is used in deep venous thrombosis.

Lepirudin is a recombinant derivative of hirudin (secreted by salivary glands of leech). It inhibits thrombin directly.

Oral Anticoagulants

They act by interfering with synthesis of vitamin K dependent clotting factors in liver. They act as competitive antagonists of vitamin K and reduce plasma levels of clotting factors in a dose dependent manner. They act by interfering with regeneration of active form of vitamin K. Factor VII levels are reduced first followed by factor IX, X and II. Warfarin is the most commonly used oral anticoagulants employed for long term anticoagulant therapy.

5.3.4 Thrombolytics

These are agents used to lyse clot and recanalise occluded blood vessels. The most important indications are coronary artery occlusion, deep vein thrombosis, etc. The agents most commonly used are streptokinase, urokinase and alteplase.

5.3.5 Platelet Inhibiting Drugs

These drugs interfere with platelet function and may be useful in prophylaxis of thromboembolic disorders. Abciximab is indicated for platelet aggregation inhibition as adjunct to percutaneous transluminal coronary angioplasty or atherectomy (PTCA). Aspirin in small doses inactivates irreversibly platelet enzyme cyclooxygenase, hence thromboxane A_2 is not synthesised. It is indicated in prophylaxis in cases of increased risk of blood clotting, myocardial infarction, coronary bypass and unstable angina.

SAQ 3

a) _____ is an abnormal state of haemostasis leading to the formation of arterial and venous thrombus, also known as _____ and _____ thrombus respectively.

b) Factor 4 is _____.

c) What is heparin?

5.4 ANTIHYPERLIPIDEMIC AGENTS

These are the drugs used for treatment of hyperlipidemia. They lower the levels of lipoproteins and lipids in blood. The plasma lipids are present in lipoproteins after combining with apoproteins. They are high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL).

Atherosclerosis is main cause of cardiovascular deaths. It is characterized by a localized plaque in the intima composed of cholesterol esters, deposition of fibrous proteins and calcification. These plaques may narrow the arterial lumen and can cause distal ischemia. The coronary and cerebral circulation, are main sites of atherosclerosis. Raised levels of VLDL, LDL and IDL are atherogenic, while HDL is protective because it facilitates removal of cholesterol from tissues.

The important drugs used in the treatment of hyperlipidemia are discussed below.

5.4.1 HMG Co-A Reductase Inhibitors

These agents are also known as statins. HMG Co-A (HMG Co-A) inhibitors block the synthesis of cholesterol in liver by competitively inhibiting HMG Co-A reductase activity. This enzyme catalyzes the conversion of HMG Co-A to mevalonate in liver which is an important early and rate limiting step in the cholesterol synthesis. As a result the cholesterol synthesis is decreased.

5.4.2 Fibric Acid Derivatives

These agents activate the enzyme lipoprotein lipase which is a key enzyme in degradation of VLDL resulting in lower circulating triglycerides. These drugs lower triglyceride levels, decrease LDL cholesterol and increase in HDL cholesterol.

5.4.3 Nicotinic Acid

Nicotinic acid reduces production of VLDL by liver, thus its degradation products IDL and LDL are subsequently reduced. It inhibits lipolysis in adipose tissue and increases activity of lipoprotein lipase. It has no effect on cholesterol and bile acid metabolism.

5.4.4 Resins (Cholestyramine and Colestipol)

They are useful only in hyperlipoproteinemias involving elevated levels of LDL. They are basic ion exchange resins.

5.4.5 Miscellaneous Drugs

Probucol

It is cholesterol lowering agent with antioxidant property. It reduces the serum cholesterol levels without reduction in serum triglycerides level and also reduces the HDL levels. It has no effect on VLDL and triglyceride levels.

Gugulipid

Is an indigenous drug obtained from gum guggul used for treatment of hyperlipidemia, hypercholesterolemia and hypertriglyceridemia.

SAQ 4

a) HMG Co-A reductase inhibitors block the conversion of _____ to _____.

b) _____ inhibit the enterohepatic circulationof bile acids and increases their excretion in faeces.

c) _____ is a cholesterol lowering agent with antioxidant property.

5.5 SUMMARY

- Anaemia is the decrease in number of red blood cells or haemoglobin content caused by blood loss, deficient erythropoiesis, excessive hemolysis, or combination of these changes. Iron deficiency anaemia is probably the most common.

- Plasma substitutes/expanders are high molecular weight substances when infused intravenously into blood stream retain fluid in the vascular compartment and exert osmotic pressure. They are used in conditions where blood plasma has been lost e.g. shock, burn cases, severe trauma and extensive tissue damage as a temporary measure till the blood can be arranged. These do not have O_2 carrying capacity. Dextrans are most commonly used plasma expanders.

- Coagulants are the agents that promote coagulation and are mainly used in any haemorrhagic condition.

- Anticoagulants are the drugs used to reduce the coagulability of blood.

- Heparin acts by activating plasma antithrombin III which rapidly inhibits activated coagulation factors Ixa, Xa, XIa and XIIa, plasmin, kallikrein and thrombin, thus inhibiting conversion of fibrinogen to fibrin.

- Statins block the synthesis of cholesterol in liver by competitively inhibiting HMG CoA reductase activity.

- Fibric acid derivatives activate lipoprotein lipase which is a key enzyme in degradation of VLDL resulting in lower circulating triglycerides.

5.6 TERMINAL QUESTIONS

1. What do you mean by haematinics? What are the main forms of iron that are used clinically?
2. What is the mechanism of action of eythropoietin and what are its therapeutic uses?
3. What are plasma expander?
4. Eplain the mechanism of action of heparin.
5. Explain the mechanism of action of vitamin K.
6. What are platelet activation inhibitors?
7. Explain the mechanism of action and uses of HMG Co-A reductase inhibitors.

5.7 ANSWERS

Self Assessment Questions

1. a) 3.5g
   b) Transferrin
   c) Desferrioxamine mesylate
   d) Erythropoietin

2. a) Dextrans
   b) Do not
   c) Anaemia is the decrease in number of red blood cells or haemoglobin content caused by blood loss, deficient erythropoiesis, excessive hemolysis, or combination of these changes.

3. a) Thrombogenesis, white, red
   b) Calcium
   c) Heparin is a heterogenous mixture of sulfated mucopolysaccharides

4. a) HMG Co-A, mevalonate
   b) Resins
   c) Probucol.

Terminal Questions

1. Hematinics are substances that are required for the formation of normal blood cells in the body. These include substances like iron, vitamin B 12, folic acid, etc.

The different iron preparations available for clinical use are as follows: Ferrous sulphate, Ferrous gluconate, Ferrous fumarate, Colloidal ferric hydroxide (50% iron), and Parenteral preparations: Iron dextran & Iron sorbitol citric acid complex.

2. Erythropoietin stimulates proliferation, maturation and haemoglobin formation by committed erythroid progenitors.Recombinant human erythropoietin is available. It is given by parenteral route (iv or sc). It **is used in** the treatment of anaemia of chronic renal failure, in anaemia of patients with AIDS who are being treated with zidovudine and anaemia associated with cancer chemotherapy.

3. Plasma substitutes/expanders are high molecular weight substances when infused intravenously into blood stream retain fluid in the vascular compartment and exert osmotic pressure. They are used in conditions where blood plasma has been lost e.g. shock, burn cases, severe trauma and extensive tissue damage as a temporary measure till the blood can be arranged. These do not have O_2 carrying capacity.

4. The biological activity of heparin is dependent upon the plasma protease inhibitor antithrombin III, which inhibits clotting factor proteases by forming equimolar stable complexes with them. It acts by activating plasma antithrombin III which rapidly inhibits activated coagulation factors Ixa, Xa, Xia and XIIa, plasmin, kallikrein and thrombin, thus inhibiting conversion of fibrinogen to fibrin.

5. Vitamin K is a fat soluble vitamin found primarily in leafy green vegetables. Most of the vitamin K is synthesized by intestinal microorganisms. Vitamin K is necessary for final stage of synthesis of coagulation factors (mainly factor II, VII, IX and X) in liver.

6. These drugs interfere with platelet function and may be useful in prophylaxis of thromboembolic disorders. The clinically used drugs are:

   Abciximab: it is indicated for platelet aggregation inhibition as adjunct to percutaneous transluminal coronary angioplasty or atherectomy (PTCA).

   Aspirin: In small doses aspirin inactivates irreversibly platelet enzyme cyclooxygenase, hence thromboxane a_2 is not synthesised. It is indicated in prophylaxis in cases of increased risk of blood clotting, myocardial infarction, coronary bypass, transluminal angioplasty, stroke, transient ischaemic attack and unstable angina.

7. Also known as statins. HMG CoA reductase inhibitors block the synthesis of cholesterol in liver by competitively inhibiting HMG CoA reductase activity which is the enzyme that catalyzes the conversion of HMG CoA to mevalonate in liver which is an important early and rate limiting step in the cholesterol synthesis. Statins are indicated as an adjunct to diet to reduce elevated total cholesterol, LDL-cholesterol and TG levels in patients with primary hypercholesterolemia, diabetic dyslipidaemia, hypertriglyceridemia, and other hyperlipidemic states.