CHAPTER 8

DRUGS ACTING ON THE BLOOD

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Ch.Id:-ASU/NSP/EB/HOP/2022/Ch-08

DOI: https://doi.org/10.52458/9789391842529.nsp2022.eb.asu.ch8

INTRODUCTION

Hematopoiesis, or the synthesis of circulating erythrocytes, platelets, and leukocytes from undifferentiated stem cells, is a remarkable process that produces about 200 billion new cells per day in a healthy person and much more blood cells in those who have blood cell loss or destruction. In adults, the hemopoietic machinery is mostly found in the bone marrow, and it requires a steady supply of three critical nutrients: iron, vitamin B12, and Folic Acid.

ANEMIA: a lack of oxygen-carrying erythrocytes that is very common in underdeveloped countries.

Anemia due to deficiency of iron, vitamin B12, or folic acid will be addressed in this section.

AGENTS USED IN ANEMIAS

IRON

Iron is the nucleus of the iron porphyrin heme ring, which, when combined with globin chains, creates hemoglobin, which binds oxygen reversibly and is responsible for oxygen distribution from the lungs to other tissues. Microcytic hypochromic anemia is caused by the formation of small erythrocytes with inadequate hemoglobin due to the absence of iron. Anemia caused by inadequate of iron, vitamin B12, or folic acid is addressed in this section.

Causes of Iron Deficiency Anemia

1. **Nutritional deficiency**

Low consumption of iron-rich foods, poor absorption due to mucosal damage, co-administration of iron-chelating medications such as antacids, and iron deficit following gastrectomy will all contribute to iron deficiency.

2. **Chronic blood loss**

Chronic nose bleeding, Menorrhagia, Occult GI bleeding, Worm infestation and Ulers, e.g. Peptic Ulcer Disease will cause iron deficiency.

PHARMACOKINETICS OF IRON

Daily Requirement of Iron: Male- 10mg, Female- 15 mg,

Daily requirement of iron increases in growing children, pregnant and lactating women

Sources

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

Body composition of Iron

Total content of Iron in the body is about 4000mg in an adult male, of which about 2/3 – 2500 mg is present in circulating red blood cells.

Table 8.1: Iron distribution in normal adults (mg)

	Men	Women
Hemoglobin	3050 mg	1700 mg
Myoglobin	430 mg	30 mg
Enzymes	10 mg	8 mg
Transport (transferrin)	8 mg	6 mg
Storage (ferritin and other form)	750 mg	300 mg
Total	4216 mg	2314 mg

N.B. The above estimations are based on the assumptions that: The average male adult weighs 80 kg and has a mean Hb level of 16 g/dL and the female adult weighs 55 kg and has a mean Hb level of 14 g/dL.

Absorption

The duodenum and proximal jejunum absorb iron. A healthy person with no iron shortage absorbs 5-10% of their daily dose. Absorption is increased in conditions when there are more requirements or shortfalls (poor iron reserves, pregnancy, menstruation, growing children, and blood loss) and/or dietary components such heme-iron (from meat, for example), HCl, and vitamin C. Non-heme iron (Fe3+) absorption is reduced in the presence of phytates, antacids, and other chelates, as well as after gastric resection.

Iron is transferred across the stinal mucosal cell by active transport, and then it is either available to transferrin for transport to plasma or stored in the mucosal cell as ferritin, depending on the mucosal iron storage. Storage: Iron is stored primarily as ferritin in intestinal mucosal cells and in macrophages in the liver, spleen and bone.

Elimination

Exfoliation of intestinal mucosal cells excretes a very little amount in stool, and trace amounts are eliminated in bile, urine, and sweat, with total daily excretion of less than 1 mg/day.

TREATMENT OF IRON DEFICIENCY ANEMIA

Whenever possible, the cause should be identified and treated. The administration of an oral or parenteral iron supplement is used to treat iron deficiency anemia.

3. Oral Iron Therapy:

Due to the most efficient absorption, only ferrous salts should be utilized. The most popular oral iron formulations include ferrous sulphate, ferrous gluconate, and ferrous fumarate. To restore iron shortage as quickly as possible, 200-400mg elemental irons should be administered daily. To replace iron stores, the treatment should be continued for 3-6 months. Side effects: Oral iron therapy can cause nausea, vomiting, epigastric discomfort, abdominal cramps, constipation and diarrhea.

4. Parenteral iron therapy:

If a patient is unable to tolerate or absorb iron from oral sources, this option should be considered. Patients with severe chronic blood loss, such as those with post-gastrectomy conditions, previous small intestine resection, inflammatory bowel illness affecting the proximal small bowel, and malabsorption syndromes, require parenteral iron therapy.

Drugs for parenteral administration include:

- Iron dextran
- Iron sorbitol

They may be given by deep intramuscular or occasionally intravascular. Intravenous administration may result in very severe allergic reactions and thus should be avoided if possible. Side effects include local pain, tissue staining, headache, light headedness, fever, arthralgia, nausea, vomiting, urticaria, back pain, bronchospasm, and rarely anaphylaxis and death.

ISBN- 978-93-91842-52-9

Acute iron Toxicity

It is only observed in small children who consume a large number of iron tablets, and it is only rarely seen in adults. Signs and symptoms: Necrotizing gastroenteritis with vomiting, abdominal pain and bloody diarrhea, shock, metabolic acidosis, coma Treatment: Whole bowel irrigation and deferoxamine, a potent iron chelating compound should be given systemically to bind iron and promote excretion through urine.

VITAMIN B12

A porphyrin-like ring with a centre cobalt atom connected to a nucleotide makes up vitamin B12. The daily need for vitamin B12 is 2-5 mg. It is primarily derived from animal products and functions as a cofactor in vital metabolic reactions in humans. Microbial production is the ultimate source of vitamin B12.

Pharmacokinetics

Once absorbed, vitamin B12 is carried to various cells of the body attached to plasma glycoprotein, transcobalamin II, after being coupled with intrinsic factor released by the stomach through a very unique receptor mediated transport pathway. Vitamin B12 excess is taken to the liver for storage and then eliminated in the urine. Clinical uses: Vitamin B12 is used to treat or prevent vitamin B12 deficiency. Deficiency of vitamin B12 results in megaloblastic anemia and neurological syndrome involving spinal cord and peripheral nerves.

Causes

Defective secretion of intrinsic factor, which is required for vitamin B12 absorption, partial or whole gastrectomy, illnesses of the distal ileum, malabsoption syndrome (such as inflammatory bowel disease, small intestinal resection, etc.) are all causes of Pernicious anemia. Almost all cases of vitamin B12 deficiencies are caused by malabsorption.

Treatment

Vitamin B12 therapeutic preparations are cyanocoblamin and hydroxycobalamin and for intrinsic factor deficiency the vitamin should be given parenterally and patients with pernicious anemia will need life-long therapy.

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FOLIC ACID

Folic acids are needed for metabolic reactions that give precursors for amino acid, purine, and DNA synthesis. 50-100g is the daily need. Folic acid insufficiency is a prevalent problem. Sources: yeast, liver, kidney and green vegetables. Physiologic functions: It is necessary for the production of purines and pyrimidines, i.e., DNA.

Folic acid → dihydrofolate→tetrahdyroflate→ precursor of purines and pyrimidines→ DNA

Pharmacokinetics

In the proximal jejunum, unaltered folic acid is absorbed quickly and completely. The liver and other tissues store 5-20 mg of folates. Because body stocks of folates are low and daily requirements are high, folic acid insufficiency and megaloblastic anaemia can develop within 1 -6 months of folic acid discontinuation. Folates are excreted in the urine and stool.

Deficiency: Patients who are elderly, poor, and pregnant women are at risk. Megaloblastic anaemia is the outcome. Folate deficiency during pregnancy can also result in congenital malformations in newborns, such as spina bifida.

Causes

Dietary deficiency, alcoholics with liver disease, hemolytic anemia, malabsorption syndrome, Patients with cancer, leukemia, myeloproliferative disorders, chronic skin diseases, patients on renal dialysis, and patients on medicines that inhibit absorption or metabolism, such as phenytoin, oral contraceptives, isoniazid, methotrexate, and others.

Treatment

Folic acid 1 mg orally per day.

N.B: - Folic acid supplementation to prevent folic acid deficiency should be considered in high-risk individuals including pregnant women, alcoholics and patients with hemolytic anemia, liver disease, certain skin disease, and patients on renal dialysis.

Even while it will mainly treat the anemia produced by the vitamin B12 deficiency, folic acid therapy in the setting of vitamin B12 insufficiency will not avoid neurological manifestations.

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DRUGS USED IN DISORDER OF COAGULATION

Introduction

Hemostasis occurs when a damaged blood vessel stops bleeding on its own.

Steps: Vascular injury → vasospasm → platelet adhesion→ platelet aggregation → activation of coagulation Cascades → Formation of "fibrin plug" or the final clot.

Anticoagulants are the drugs which inhibit fibrin formation.

Classification

Based on mechanism of action

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

HEPARIN

It is a heterogeneous mixture of sulfated mucopolysaccharides. Mechanism of action Heparin activates antithrombin III (AT III), which inhibits clotting factor proteases and, as a result, prevents the production of fibrin clots, the conversion of fibrinogen to fibrin, and the inactivation of many factors involved in blood clotting.

Clinical Uses

Prevention and treatment of venous thrombosis, atrial fibrillation with embolus production, prevention of post-operative thrombosis and embolism in open heart surgery, treatment of coronary occlusion, acute myocardial infarction, and peripheral arterial embolism.

Administration

It can be administered intravenously or subcutaneously. Oral therapy is unsuccessful because gastric acids inactivate it, and absorption is low due to the high molecular size. Because of the risk of hematoma formation at the injection site, heparin should never be given intramuscularly.

Side effects

Bleeding is the major side effect, allergy, alopecia, osteoporosis and thrombocytopenia.

Contraindications

Contraindicated in patients who are hypersensitive to the drug, are actively bleeding or have hemophilia, thrombocytopenia, and purpura, sever hypertension, intracranial hemorrhage, infective endocarditis, active tuberculosis, etc.

ORAL ANTICOAGULANTS

WARFARIN

Originally, this substance was used as a rodent poison. It is the most extensively used coumarin anticoagulant and may be regarded the anticoagulant of choice for oral usage.

Mechanism of action

The anticoagulant blocks the inactive vitamin K epoxide from being reductively converted to its active form, resulting in a depletion of the reduced form of vitamin K, which serves as a cofactor for gamma carboxylation of vitamin K-dependent coagulation factors.

Pharmacokinetics

It is taken orally as a sodium salt and has a 100% bioavailability. Because 99 percent of the drug is bound to albumin, it has a sluggish onset of effect and a long half-life in plasma (36 hours).

Clinical uses

Prevention and treatment of deep vein thrombosis, treatment of atrial fibrillation with thrombus formation, prevention and treatment of pulmonary embolus, as part of the treatment of coronary occlusion and prevention of thrombus formation after value replacement

Side effects

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

Contraindications

similar to heparin and the drug should never be administered during pregnancy.

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Drug interactions

When warfarin is used with the following medicines, its effectiveness is increased: cimitidine, dsulfiram, metronidazole, phenylbutazone, acetyl salicylic acid and cephalosporin (3rd generations)

When warfarin is used with the following medicines, its effectiveness is reduced: barbiturates, cholestyramine, rifampincin, diuretics, and vitamin K

THROMBOLYTIC AGENTS

By catalysing the synthesis of plasmin from plasminogen, fibrinolytic drugs rapidly lyse thrombi. All current thrombolytic drugs function as plasminogen activators, either directly or indirectly. The plasminogen activators currently in use are:

a. Streptokinase- a streptococcal protein that binds to plasminogen and converts it to active plasmin.
b. Urokinase- The kidneys produce a human enzyme that converts plasminogne to active plasmin.
c. Anistreptase (Acylated plasminongen -streptokinase activator) - human plasminogen with bacterial streptokinase
d. Tissue Plaminogen Activator (TPA) - This activates plasminogen attached to fibrin in a preferred manner.

Indications: Multiple pulmonary emboli, central deep vein thrombosis and acute myocardial infarction.

Adverse Reactions: Bleeding and allergic reactions are most common adverse effects of thrombolytic.

Contra-indications: Severe hypertension, recent cranial trauma and history of cerebrovascular accident.

ANTIPLATELET DRUGS

Platelet function is regulated by three categories of substances

1. Agents outside the platelet that interact with platelet membrane receptors e.g. catecholamines, prostacyclin
2. Agents generated within the platelets and interact with the membrane receptors, e.g. prostaglandin E2 and serotonin

3. Agents generated within the platelet and act within the platelet, e.g. thromboxane A2 and calcium ions

Antiplatelets act on any one of the above processes. They include aspirin, ticlopidine, dipyridamole.

ASPIRIN (ASA)

The arachidonate product thromboxane A2 causes platelets to alter shape, release their granules, and aggregate. Platelet aggregation is inhibited by drugs that block this mechanism, which prolongs bleeding time. The low-dose asprin is the prototype of this class. By irreversibly acetylating the enzyme cyclo-oxygenase, it suppresses the formation of thromboxane A2.

Therapeutic Uses

Prevention of myocardial infarction and stroke in patients at risk, such as those who have had transient ischemic episodes.

ISBN- 978-93-91842-52-9