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25.

DRUGS AFFECTING BLOOD

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25.1 Introduction

The circulatory system has a number of important physiological functions. These include transport of metabolites, hormonal and temperature regulation and protection against disease. All of the molecules needed for normal cellular metabolism are transported in the blood. Red blood cells carry oxygen to tissues and remove carbon dioxide waste gases. In addition, the blood carries nutrients from digestion and absorption of foodstuffs to target cells and removes excess water and unwanted waste products of cellular metabolism to the kidney for excretion. Blood also transports hormones and other cellular control molecules from site of synthesis to their site of action and is involved in body temperature regulation. Furthermore the circulatory system aids in protection against foreign invasion by toxin or bacteria through protective white blood cells (leukocytes), whilst clotting mechanisms protect against blood loss when the blood vessels of the circulatory system are damaged.

Blood comprises two portions, a cellular component termed the “formed elements” and a “fluid component” termed plasma. The plasma is a pale yellow fluid that consists of water, dissolved solutes, soluble metabolites, hormones, antibodies and other proteins including the albumins and globulins which are used to transport molecules around the body and

fibrinogen, which is an important clotting factor. Within the "formed elements" are the cellular components of blood including the erythrocytes (used to transport oxygen via haemoglobin), platelets (involved in blood clotting) and the leukocytes (which comprise neutrophils, eosinophils, basophils, monocytes and lymphocytes and whose roles include phagocytosis and the release of antibodies as an immune response).

25.2 Important dysfunctions of the blood system

There are a number of pathophysiological conditions associated with dysfunctions of the circulatory system (see Figure at end of this eChapter). The major problems are thrombosis (the formation of an unwanted clot within the blood vessels or heart), uncontrolled bleeding (as a result of a disease or injury) and anaemia (caused by disease or nutritional deficiencies). Other problems that can arise include cancers associated with components of the circulatory system (for example, leukaemia, lymphoma), diseases resulting in reduced or increased functioning of the immune system (rheumatoid arthritis, systemic lupus) and hyperlipidaemias. These are covered elsewhere.

25.3 Drugs used in to correct dysfunctions of the blood

25.3.1 Anti-thrombosis treatments

Thrombosis occurs when there is formation of an unwanted blood clot (thrombus) or movement of an existing clot to a location where it can block important blood vessels. When there is damage to a blood vessel, a number of co-ordinated processes occur, resulting in the formation of a fibrin-platelet thrombus plug that facilitates cessation of bleeding (haemostasis) at the site of injury. This process includes movement of platelets to the site of injury and their adhesion to, and covering of, the exposed collagen of the subendothelial tissues via binding to von Willebrand factor and glycoprotein Ib (GpIb). The platelets then become active and release a variety of chemoattractants including ADP, thromboxane A2, serotonin and platelet activating factor (PAF) which in turn mobilise other platelets to the site of injury where they begin to adhere and aggregate into the growing clot via GpIIb/IIIa platelet receptors. Fibrinogen, a soluble plasma protein, simultaneously binds to GpIIb/IIIa receptors on two separate platelets resulting in platelet crosslinking and further platelet aggregation. Activation of the clotting cascade ultimately results in thrombin production from its precursor prothrombin. Thrombin, in turn, converts fibrinogen in the growing thrombus to fibrin, consolidating and stabilising the platelet plug.

There are three drug treatments used to prevent formation of clots or to dissolve established thrombi. These are the anti-platelet drugs, the anticoagulents and the thrombolytics.

25.3.1.1 Platelet aggregation inhibitors

The **anti-platelet drugs** (or p**latelet aggregation inhibitors**) work by decreasing the synthesis, release or action of the chemical molecules that promote platelet aggregation preventing clot formation. **Aspirin** inhibits cyclooxygenase-1 (COX-1), the enzyme responsible for the production of thromboxane A2 from arachidonic acid, thus blocking the synthesis of the aggregating agent. The main adverse effects of aspirin administration are gastrointestinal ulcers, stomach bleeding and tinnitus.

Another drug which targets thromboxane A2 synthesis is **dipyridamole** which is a cyclic nucleotide phosphodiesterase inhibitor. Dipyridamole increases intracellular cyclic AMP levels which results in decreased thromboxane A2 synthesis. This agent is usually given in combination with aspirin or warfarin.

Clopidogrel is approved for the prevention of atherosclerotic events following recent myocardial infarction, stroke or established peripheral vascular disease. Clopidogrel selectively inhibits the binding of ADP to its platelet receptor, an event that leads to inhibition of platelet aggregation by blocking activation of the GpIIb/IIIa pathway.

Working in a similar way, **abciximab** is a monoclonal antibody that is indicated for percutaneous coronary intervention (angioplasty). It binds to the platelet GpIIb/IIIa receptor, preventing binding of von Willebrand factor, fibrinogen, and other adhesion molecules inhibiting receptor-mediated platelet activation and subsequent thrombus formation. The major adverse effect is potential for bleeding.

Eptifibatide and **tirofiban** have similar indications, adverse reactions and mechanisms of action to abciximab except that they are not antibodies but chemical antagonists of the GpIIb/IIIa receptor.

25.3.1.2 Anticoagulants

The second group of antithrombosis drugs are the **anticoagulants**. In the process of forming a thrombus, fibrinogen is converted to fibrin by thrombin, the end point of the clotting cascade. The cascade is a series of reactions that sequentially transform various plasma fractions to their active enzymic form. They ultimately produce activated clotting factor Xa which converts prothrombin to thrombin. Anticoagulants exert their action by reducing the action of specific clotting factors, as in the case of the heparins, or by interfering with clotting factor synthesis, as demonstrated by the vitamin K antagonists.

Heparin and its lower molecular weight forms (**enoxaparin, dalteparin**) exert their effects by binding to and activating antithrombin III. Activation of this enzyme results in thrombin inactivation and subsequent blocking of clot formation. These drugs are indicated for deep vein thrombosis, pulmonary embolism and acute coronary syndrome. Adverse effects of the heparins include haemhorrage and thrombocytopaenia.

The coumarin anticoagulants (**warfarin**) exert their actions by inhibiting the synthesis of vitamin K dependent coagulation factors (VII, IX, X, II) perturbing the clotting cascade. They are used to prevent the progression or recurrence of deep vein thrombosis and pulmonary embolism. The main adverse reaction to warfarin treatment is haemorrhage. Warfarin has numerous drug interactions that may potentiate or attenuate its actions. As such warfarin administration should be monitored closely.

25.3.1.3 Thrombolytics

The last group of antithrombosis drugs are the **thrombolytics** (**fibrinolytics**). These drugs are used to dissolve clots that have already formed. They are usually administered intravenously to clear a blocked blood vessel (for example in coronary thrombosis) and work by promoting the conversion of plasminogen to plasmin, a serine protease enzyme that hydrolyses fibrin, dissolving the clot, allowing reperfusion to occur.

The first drug in this class to be used was **streptokinase**, a protein isolated from beta-haemolytic *Streptococc*i. Streptokinase activates plasminogen and promotes its conversion to plasmin. However, streptokinase causes a systemic fibrinolytic effect that can lead to bleeding problems and this agent has been replaced by tissue-type plasminogen activators (tPAs) such as **alteplase**, **tenecteplase** and **reteplase.** These agents have been produced by recombinant DNA technology and work locally on the thrombotic fibrin to produce

fibrinolysis. Bleeding complications including gastrointestinal haemorrhage and stroke have been shown to occur with their use.

25.3.2 Treatments for anaemia

Anaemia is a condition where there is decreased plasma haemoglobin levels resulting from either a decreased number of circulating red blood cells or a deficiency of functioning haemoglobin within the erythrocytes themselves. This impacts on the capacity of the red blood cells to transport oxygen and nutrients to target tissues. There are a number of different types of anaemias, each characterised by the condition of their red blood cells. In microcytic anaemias (iron deficiency, sideroblastic anaemia) the erythrocytes are smaller than normal ;: in normocytic anaemia (bone marrow failure, endocrine anaemia), cells are normal sized; in macrocytic anaemia (pernicious anaemia, folic acid deficiency, megaloblastic anaemia), cells are larger than normal; whilst in haemolytic anaemia (haemaglobinopathies, infections), the cells have autolysed. All of these anaemic states cause similar symptoms such as pallor, shortness of breath and fatigue.

Normal erythropoeisis requires a number of factors such as iron, vitamin B12 and folic acid, and a deficiency in any of these can cause anaemia. The main therapeutic approach to treating anaemia relies on replacing such deficiencies.

Iron deficiency is a common cause of anaemia and can result from chronic blood loss (e.g. menorrhagia (heavy blood loss during menstrual periods)), from gut abnormalities resulting in reduced iron absorption and in heavily menstruating or pregnant women. Iron deficiency syndromes can be treated with oral or parental **iron salt** (**ferrous sulphate**, **ferrous gluconate**, **ferrous glycine sulphate**) supplementation. Gastrointestinal disturbances, particularly constipation are the most common side effects of these treatments.

Vitamin B12 deficiency, either as a result of poor absorption of the vitamin itself or more commonly, failure to produce the intrinsic factor needed for vitamin B12 function, results in megaloblastic and pernicious anaemias. Treatment is by administration of various **colbalamins** (**methylcobalamin**, **cyanocobalamin**, **hydroxocobalamin**) which are chemically related forms of vitamin B12.

Folic acid is required for DNA and amino acid synthesis. Deficiency can be caused by increased folate demand during pregnancy and lactation, poor absorption caused by disease of the small intestine, alcoholism or concomitant treatment with folate inhibitor drugs such as methotrexate. Folica acid deficiencyleads to megaloblastic anaemia. Treatment is by oral **folic acid** administration.

Erythropoietin is a glycoprotein hormone, produced in the kidney, that regulates red blood cell proliferation and differentiation in the bone marrow. Recombinant human erythropoietin and **darbepoetin**, a variant with a longer half-life, are used to treat anaemias resulting from chronic kidney disease and from some chemotherapy treatments, particularly the platinum-containing anticancer drugs.

Sickle cell anaemia is a hereditary disorder in which a point mutation in one haemoglobin chains results in a valine being substituted for a glutamic acid. This haemoglobin, HbS, becomes sickle shaped when oxygenated resulting in impaired erythrocyte function. Treatment is with **hydroxyurea** which activates production of foetal haemoglobin, a process that occurs over many months, diluting the abnormal HbS.

25.3.3 Treatments for bleeding disorders

Uncontrolled bleeding occurs as a consequence of either a hereditary disease (haemophilia A, haemophilia B, von Willebrand's disease) or an acquired condition (vitamin K deficiency, thrombocytopaenia, fibrinolysis after surgery).

Hereditary bleeding disorders
Haemophilic disease occurs as a result of a genetic lesion affecting one or more factors in the clotting cascade. Previous treatments involved administration of concentrated preparations of these factors isolated from donated human blood, a practice used less today with the ability of recombinant DNA technology to produce large amount of these components. Thus haemophilia A is treated with administration of **clotting factor VIII** and haemophilia B with **clotting factor IX**.

Acquired bleeding disorders
Treatment of acquired, uncontrolled bleeding is more problematical. In general, these episodes are caused by an individual being in a fibrinolytic state and treatment negates the cause of bleeding or potentiates the clotting mechanism.

Vitamin K1 administration promotes the formation of various clotting factors (II, VI, IX, X) and can reverse an abnormal coagulation status (for example treatment after surgery) or bleeding due to vitamin K1 deficiency.

Protamine sulphate is a heparin antagonist and is used to counteract the effect of this drug before and after surgery.

Tranexamic acid is a competitive inhibitor of the plasminogen activation process resulting in decreased production of plasmin and subsequent plasmin-mediated fibrinolysis. It is used to treat menorrhagia and patients with clotting disorders undergoing surgery. However, a potential side effect of treatment with tranexamic acid is intravascular thrombosis.

Similarly, **aprotinin** a serine protease used to reduce perioperative blood loss, also stops bleeding by blocking the action of plasmin.