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Lecture 8 and 9

Blood Dysfunctios

Blood Dysfunctios:

This lectuter describes drugs that are useful in treating disorders of hemostasis.

Thrombosis, the formation of an unwanted clot within a blood vessel, is the most common abnormality of hemostasis.

Thrombotic disorders include:

1. Acute myocardial infarction (MI).
2. Deep vein thrombosis (DVT).
3. Pulmonary embolism (PE).
4. Acute ischemic stroke.

These conditions are treated with drugs such as anticoagulants and fibrinolytics.

Bleeding disorders involving the failure of hemostasis are less common than thromboembolic diseases.

These disorders include **hemophilia**, which is treated with transfusion of recombinant factor VIII.

Vitamin K deficiency, which is treated with vitamin K supplementation.

Thrombus Versus Emolus:

A clot that adheres to a vessel wall is called a "thrombus" , whereas an intravascular clot that floats in the blood is termed an "embolus" .

Thus, a detached thrombus becomes an embolus. Both thrombi and emboli are dangerous, **because they may occlude blood vessels and deprive tissues of oxygen and nutrients**.

Arterial thrombosis most often occurs in medium-sized vessels rendered thrombogenic by atherosclerosis, arterial thrombosis usually consists of a platelet-rich clot.

In contrast, **venous thrombosis** is triggered by blood stasis or inappropriate activation of the coagulation cascade. Venous thrombosis typically involves a clot that is rich in fibrin, with fewer platelets than are observed with arterial clots.

1.Platlet Aggregation Inhibitores:

Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation.

1. **Aspirin:**

Therapeutic use: Aspirin is used in the

a. Prophylactic treatment of transient cerebral ischemia.
b. To reduce the incidence of recurrent MI, and to decrease mortality in the setting of primary and secondary prevention of MI.

Complete inactivation of platelets occurs with 75 mg of aspirin given daily. The recommended dose of aspirin ranges from 50 to 325 mg daily.

Adverse effects: Higher doses of aspirin increase drug-related toxicities as well as bleeding time is prolonged by aspirin

treatment and gastrointestinal (GI) bleeding may occure if gastric and, or intestinal ulcer present.

2. **Clopidogrel.**

ADP(adenosine di phosphate) receptor inhibitors that also block platelet aggregation but by a mechanism different from that of aspirin.

Therapeutic use: Clopidogrel is approved for prevention of
1.Atherosclerotic events in patients with a recent MI or stroke.

2.in those with established peripheral arterial disease.

3.It is also approved for prophylaxis of thrombotic events in acute coronary syndromes (unstable angina or non–ST-elevation MI).

4.Additionally, clopidogrel is used to prevent thrombotic events associated with percutaneous coronary intervention (PCI) with or without coronary stenting.

Adverse effects:

Clopidogrel can cause prolonged bleeding for which there is no antidote but with less side effects than others.

2. Anticoagulalents :

Heparin and low molecular weight heparins(LMWHs).

Heparin is an injectable, rapidly acting anticoagulant that is often used acutely to interfere with the formation of thrombi.

The **LMWHs** are heterogeneous compounds about one-third the size of unfractionated heparin, **enoxaparin** produced by enzymatic depolymerization of unfractionated heparin.

Therapeutic use: Heparin and the LMWHs limit the expansion of thrombi by preventing fibrin formation. These agents are used for the treatment of acute venous thromboembolism.

Adverse effects: The chief complication of heparin and LMWH therapy is bleeding . Careful monitoring of the patient and laboratory parameters is required to minimize bleeding. Excessive bleeding may be managed by discontinuing the drug or by treating with protamine sulfate.

- **Warfarin**

The coumarin anticoagulants owe their action to the ability to antagonize the cofactor functions of vitamin K. The only therapeutically relevant coumarin anticoagulant is **warfarin**. Initially used as a rodenticide, warfarin is now widely used clinically as an oral anticoagulant.

The INR is the standard by which the anticoagulant activity of warfar

in therapy is monitored.

Therapeutic use: Warfarin is used in the prevention and treatment of DVT.

Adverse effects: The principal adverse effect of warfarin is hemorrhage, and the agent has a black box warning for bleeding risk. Therefore, it is important to frequently monitor the INR and adjust the dose of warfarin. Minor bleeding may be treated by withdrawal of the drug or administration of oral vitamin K1 , but severe bleeding may require greater doses of vitamin K given intravenously. Whole blood, frozen plasma, and plasma concentrates of blood factors may also be used for rapid reversal of warfarin.

Druges used to treat bleading.

Bleeding problems may have their origin in naturally occurring pathologic conditions, such as hemophilia, or as a result of fibrinolytic states that may arise after GI surgery or prostatectomy.

The use of anticoagulants may also give rise to hemorrhage. Certain natural proteins and vitamin K, as well as synthetic antagonists, are effective in controlling this bleeding.

A.Aminocaproic acid and tranexamic acid:

Fibrinolytic states can be controlled by the administration of aminocaproic acid or tranexamic acid. Both agents are synthetic, orally active, excreted in the urine, and inhibit plasminogen activation. Tranexamic acid is 10 times more potent than aminocaproic acid. A potential side effect is intravascular thrombosis.

B. Protamine sulfate: Protamine sulfate antagonizes the anticoagulant effects of heparin.

C. Vitamin K:

Vitamin K1 (phytonadione) administration can stop bleeding problems due to warfarin by increasing the supply of active vitamin K1 , thereby inhibiting the effect of warfarin. Vitamin K1 may be administered via the oral, subcutaneous, or intravenous route.

Drugs For Anemia.

Anemia is defined as a below-normal plasma hemoglobin concentration resulting from a decreased number of circulating red blood cells or an abnormally low total hemoglobin content per unit of blood volume.

General signs and symptoms of anemia include fatigue, rapid heartbeat, shortness of breath, pale skin, dizziness, and insomnia.

Anemia can be caused by chronic blood loss, bone marrow abnormalities, increased hemolysis, infections, malignancy, endocrine deficiencies, renal failure, and a number of other disease states.

Nutritional anemias are caused by dietary deficiencies of substances such as iron, folic acid, and vitamin B12 (cyanocobalamin) that are necessary for normal erythropoiesis.

Anemia can be at least temporarily corrected by transfusion of whole blood.

Agents Used To Treat Anemias:

A. Iron.

Iron is stored in the intestinal mucosal cells, liver, spleen, and bone marrow as ferritin (an iron–protein complex) until needed by the body. Iron is delivered to the marrow for hemoglobin production by a transport protein, namely transferrin.

Iron deficiency results from acute or chronic blood loss, from insufficient intake during periods of accelerated growth in children, and in heavily menstruating or pregnant women.

Pharmacokinetics: Iron is absorbed after oral administration. Acidic conditions in the stomach keep iron in the reduced ferrous form, which is the more soluble form.

Adverse effects: Gastrointestinal (GI) disturbances caused by local irritation (abdominal pain, constipation, diarrhea, etc.) and dark stools are the most common adverse effects of oral iron supplements. Parenteral iron formulations may be used in those who cannot tolerate oral iron. Fatal hypersensitivity and anaphylactoid reactions can occur in patients receiving parenteral iron (mainly iron dextran formulations). A test dose should be administered prior to iron dextran.

B. Folic acid (folate)

The primary use of **folic acid** is in treating deficiency states that arise from inadequate levels of the vitamin. Folate deficiency may be caused by

1) increased demand (for example, pregnancy and lactation)
2) poor absorption caused by pathology of the small intestine,
3) alcoholism.

Folic acid is well absorbed in the jejunum unless pathology is present. If excessive amounts of the vitamin are ingested, they are excreted in the urine and feces. Oral folic acid administration is nontoxic.

C. Cyanocobalamin and hydroxocobalamin (vitamin B12)

Deficiencies of vitamin B12 can result from either low dietary levels or, more commonly, poor absorption of the vitamin.