Drugs used in treatment of Cardiovascular System

Blood Drugs

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Thrombus VS. Embolus

- Thrombus: a clot that adheres to a vessel wall.

- Embolus: an intravascular clot that floats in the blood.
- Arterial thrombosis (platelet-rich clot) most often occurs in medium-sized vessels rendered thrombogenic by surface lesions on endothelial cells caused by atherosclerosis.
- Venous thrombosis (rich in fibrin) is triggered by blood stasis or inappropriate activation of the coagulation cascade, frequently as a result of a defect in the normal hemostatic defense mechanisms.

Platelet Response to Vascular Injury

A. Resting platelets

- Platelets act as vascular sentries, monitoring the integrity of the endothelium. In the absence of injury, resting platelets circulate freely, because the balance of chemical signals indicates that the vascular system is not damaged.

Chemical mediators synthesized by endothelial cells:

- prostacyclin and nitric oxide, are synthesized by intact endothelial cells and act as inhibitors of platelet aggregation. Prostacyclin (prostaglandin I_2) acts by binding to platelet membrane receptors that are coupled to the synthesis of cyclic adenosine monophosphate (cAMP). Elevated levels of intracellular cAMP are associated with a decrease in intracellular Ca^{2+}. This leads to inhibition of platelet activation and the subsequent release of platelet aggregation agents.

Roles of thrombin, thromboxanes, and collagen:

- The platelet membrane also contains receptors that can bind thrombin, thromboxanes, and exposed collagen. In the intact, normal vessel, circulating levels of thrombin and thromboxane are low, and the intact endothelium covers the collagen in the subendothelial layers. The corresponding platelet receptors are thus unoccupied and remain inactive; as a result, platelet activation and aggregation are not initiated. However, when occupied, each of these receptor types triggers a series of reactions leading to the release into the circulation of intracellular granules by the platelets. This ultimately stimulates platelet aggregation.

B. Platelet adhesion

- When the endothelium is injured, platelets adhere to and virtually cover the exposed collagen of the subendothelium. This triggers a complex series of chemical reactions, resulting in platelet activation.

C. Platelet activation

- Receptors on the surface of the adhering platelets are activated by the collagen of the underlying connective tissue.
- This causes morphologic changes in the platelets and the release of platelet granules containing chemical mediators, such as (ADP), thromboxane A_2, serotonin, PAF, and thrombin. These signaling molecules bind to receptors in the outer membrane of resting platelets circulating nearby.
- The previously dormant platelets become activated and start to aggregate-actions mediated by several messenger systems that ultimately result in elevated levels of Ca^{2+} and a decreased concentration of cAMP within the platelet.

D. Platelet aggregation

- The increase in cytosolic Ca^{2+} accompanying activation is due to a release of sequestered stores within the platelet. This leads to

1) the release of platelet granules containing mediators, such as ADP and serotonin that activate other platelets;

2) activation of thromboxane A_2 synthesis; and

3) activation of the glycoprotein (GP) IIb/IIIa receptors that bind fibrinogen and, ultimately, regulate platelet-platelet interaction and thrombus formation. Fibrinogen, a soluble plasma GP, simultaneously binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet cross-linking and platelet aggregation.

This leads to an avalanche of platelet aggregation, because each activated platelet can recruit other platelets.

E. Formation of a clot

- Thrombin (Factor IIa) catalyzes the hydrolysis of fibrinogen to fibrin, which is incorporated into the plug. Subsequent cross-linking of the fibrin strands stabilizes the clot and forms a hemostatic platelet-fibrin plug.

F. Fibrinolysis

- During plug formation, the fibrinolytic pathway is locally activated. Plasminogen is enzymatically processed to plasmin (fibrinolysin) by plasminogen activators in the tissue. Plasmin limits the growth of the clot and dissolves the fibrin network as wounds heal.

Platelet Aggregation Inhibitors

A. Aspirin

- Thromboxane A_2 produced by the aggregating platelets further promotes the clumping process that is essential to the rapid formation of a hemostatic plug.

- Aspirin inhibits thromboxane A_2 synthesis from arachidonic acid in platelets, resulting in a blockade of arachidonate to the active site and, thus, inhibition of COX-1.

- This shifts the balance of chemical mediators to favor the antiaggregatory effects of prostacyclin, thus impeding platelet aggregation. The inhibitory effect is rapid, apparently occurring in the portal circulation.

- The aspirin-induced suppression of thromboxane A_2 synthetase and the resulting suppression of platelet aggregation last for the life of the anucleate platelet-approximately 7 to 10 days.

- Aspirin is currently employed in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent myocardial infarction, and to decrease mortality in pre and post myocardial infarct patients.

- The recommended dose of aspirin ranges from 81 to 325 mg, with side effects determining the dose chosen.

- Bleeding time is prolonged by aspirin treatment, causing complications that include an increased incidence of hemorrhagic stroke as well as gastrointestinal bleeding, especially at higher doses of the drug.

B. Ticlopidine and clopidogrel

- Mechanism of action: These drugs irreversibly inhibit the binding of ADP to its receptors on platelets and, thus, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other.
- Therapeutic use:

Ticlopidine:

1. approved for the prevention of transient ischemic attacks and strokes for patients with prior cerebral thrombotic event.
2. It is also used as adjunct therapy with aspirin following coronary stent implantation to decrease the incidence of stent thrombosis.

- However, due to its life-threatening hematologic adverse reactions, including neutropenia/agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia, it is generally reserved for patients who are intolerant to other therapies.

Clopidogrel:

1. approved for prevention of atherosclerotic events following recent myocardial infarction, stroke, or established peripheral arterial disease.
2. It is also approved for prophylaxis of thrombotic events in acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction).
3. to prevent thrombotic events associated with percutaneous coronary intervention with or without coronary stent.

- Compared to ticlopidine, clopidogrel is the preferred agent in ischemic heart disease events, because there is more data to support use of clopidogrel in these cardiac patients.

- Furthermore, clopidogrel has a better overall side-effect profile, although TTP may also occur with this agent.

- Food interferes with the absorption of ticlopidine but not with clopidogrel.

- After oral ingestion, both drugs are extensively bound to plasma proteins. They undergo hepatic metabolism by the cytochrome P450 system to active metabolites that are yet to be identified.

- The maximum effect is achieved in 3 to 5 days; when treatment is suspended, the platelet system requires time to recover.

C. Abciximab

- Abciximab directed against the GP IIb/IIIa complex. By binding to GP IIb/IIIa, the antibody blocks the binding of fibrinogen and von Willebrand factor; consequently, aggregation does not occur.

- Abciximab is given intravenously along with heparin or aspirin as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications. After cessation of infusion, platelet function gradually returns to normal, with the antiplatelet effect persisting for 24 to 48 hours.

- The major adverse effect of abciximab therapy is the potential for bleeding, especially if the drug is used with anticoagulants or if the patient has a clinical hemorrhagic condition.

- Abciximab is expensive, limiting its use in some settings.

D. Eptifibatide and tirofiban

- These two antiplatelet drugs act similarly to abciximab-namely, blocking the GP IIb/IIIa receptor.

- Eptifibatide is a cyclic peptide that binds to GP IIb/IIIa at the site that interacts with fibrinogen. Tirofiban is not a peptide, but it blocks the same site as eptifibatide.

- These compounds, like abciximab, can decrease the incidence of thrombotic complications associated with acute coronary syndromes. When intravenous infusion is stopped, these agents are rapidly cleared from the plasma, but their effect can persist for as long as 4 hours.

- Eptifibatide and its metabolites are excreted by the kidney. Tirofiban is excreted unchanged by the kidney. The major adverse effect of both drugs is bleeding.

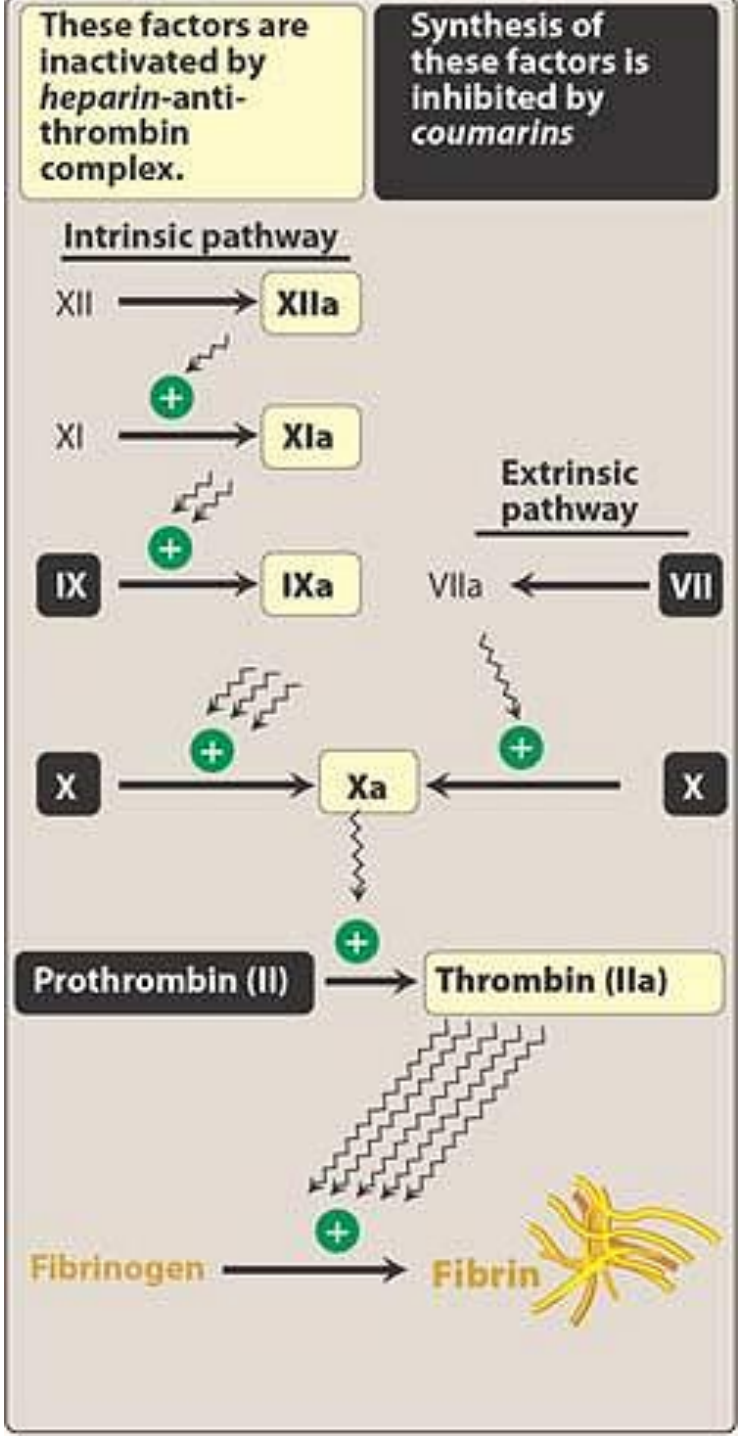
E. Dipyridamole

- Dipyridamole, a coronary vasodilator, is employed prophylactically to treat angina pectoris. It is usually given in combination with aspirin or warfarin; it is ineffective when used alone.

- Dipyridamole increases intracellular levels of cAMP by inhibiting cyclic nucleotide phosphodiesterase, resulting in decreased thromboxane A_2 synthesis. It may potentiate the effect of prostacyclin to antagonize platelet stickiness and, therefore, decrease platelet adhesion to thrombogenic surfaces.

- The meager data available suggest that dipyridamole makes only a marginal contribution to the antithrombotic action of aspirin. In combination with warfarin, however, dipyridamole is effective for inhibiting embolization from prosthetic heart valves.

Blood Coagulation



Anticoagulants

A. Thrombin inhibitors:

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. Heparin normally occurs as a macromolecule complexed with histamine in mast cells, where its physiologic role is unknown.

- The realization that low-molecular-weight forms of heparin (LMWHs) can also act as anticoagulants led to the isolation of enoxaparin, the first LMWH (<6000) available in the United States.

- Heparin is used in the prevention of venous thrombosis and the treatment of a variety of thrombotic diseases, such as pulmonary embolism and acute myocardial infarction.

Mechanism of action:

- Heparin acts at a number of molecular targets, but its anticoagulant effect is a consequence of binding to antithrombin III, with the subsequent rapid inactivation of coagulation factors.

- Antithrombin III inhibits serine proteases, including several of the clotting factors-most importantly, thrombin (Factor IIa) and Factor Xa. In the absence of heparin, antithrombin III interacts very slowly with thrombin and Factor Xa. Heparin molecules bind antithrombin III inducing a conformational change that accelerates its rate of action about 1000-fold.

- Heparin also serves as a catalytic template for the interaction of antithrombin III and the activated coagulation factors. Heparin serves as a true catalyst, allowing antithrombin III to rapidly combine with and inhibit circulating thrombin and Factor Xa.

- In contrast, LMWHs complex with antithrombin III and inactivate Factor Xa-including that located on platelet surfaces-but do not bind as avidly to thrombin. Indeed, LMWHs are less likely than heparin to activate resting platelets.

Therapeutic uses:

- Heparin and the LMWHs limit the expansion of thrombi by preventing fibrin formation.
- Heparin has been the major antithrombotic drug for the treatment of acute deep-vein thrombosis and pulmonary embolism.
- The incidence of recurrent thromboembolic episodes is also decreased.
- Clinically, heparin is used prophylactically to prevent postoperative venous thrombosis in patients undergoing elective surgery (for example, hip replacement) and those in the acute phase of myocardial infarction.
- Coronary artery rethrombosis after thrombolytic treatment is reduced with heparin.
- The drug is also used in extracorporeal devices (for example, dialysis machines) to prevent thrombosis.
- Heparin and LMWHs are the anticoagulants of choice for treating pregnant women with prosthetic heart valves or venous thromboembolism, because these agents do not cross the placenta (due to their large size and negative charge).
- Heparin has the advantage of speedy onset of action, which is rapidly terminated on suspension of therapy. However, it is being supplanted by the LMWHs, such as enoxaparin and dalteparin, because they can be conveniently injected subcutaneously on a patient weight-adjusted basis, have predictable therapeutic effects, and have a more predictable pharmacokinetic profile.

DRUG CHARACTERISTIC	*HEPARIN*	*LMWHs*
Intravenous half-life	2 hours	4 hours
Anticoagulant response	Variable	Predicable
Bioavailability:	20%	90%
Major adverse effect	Frequent bleeding	Less frequent bleeding
Setting for therapy	Hospital	Hospital and outpatient

B. Other parenteral anticoagulants

1. **Lepirudin:** A highly specific, direct thrombin antagonist, One molecule of lepirudin binds to one molecule of thrombin, resulting in blockade of the thrombogenic activity of thrombin. It has little effect on platelet aggregation. Administered intravenously, lepirudin is effective in the treatment of HIT and other thromboembolic disorders, and it can prevent further thromboembolic complications.

2. **Argatroban:** is a parenteral anticoagulant that is a small molecule that direct inhibits thrombin. Argatroban is used prophylactically for the treatment of thrombosis in patients with HIT, and it is also approved for use during percutaneous coronary interventions in patients who have or are at risk for developing HIT.

3. **Fondaparinux:** It has been recently approved by the U.S. Food and Drug Administration for use in the prophylaxis of deep-vein thrombosis that could lead to pulmonary embolism in patients undergoing hip fracture surgery, hip replacement surgery, and knee replacement surgery. This agent selectively inhibits only Factor Xa. By selectively binding to antithrombin III, fondaparinux potentiates (300- to 1000-fold) the innate neutralization of Factor Xa by antithrombin III.

C. Vitamin K antagonists: Warfarin

- **Mechanism of action**: Several of the protein coagulation factors (including Factors II, VII, IX, and X;) require vitamin K as a cofactor for their synthesis by the liver. These factors undergo vitamin K-dependent posttranslational modification, which are essential for interaction between the coagulation factors and platelet membranes.
- Warfarin treatment results in the production of clotting factors with diminished activity (10%-40% of normal).
- Unlike heparin, the anticoagulant effects of warfarin are not observed until 8 to 12 hours after drug administration, but peak effects may be delayed for 72 to 96 hours.
- The anticoagulant effects of warfarin can be overcome by the administration of vitamin K. However, reversal following administration of vitamin K takes approximately 24 hours (the time necessary for degradation of already synthesized clotting factors).

Therapeutic uses:

1. Warfarin is used to prevent the progression or recurrence of acute deep-vein thrombosis or pulmonary embolism after initial heparin treatment.
2. It is also used for the prevention of venous thromboembolism during orthopaedic or gynecologic surgery.
3. Prophylactically, it is used in patients with acute myocardial infarction, prosthetic heart valves, or chronic atrial fibrillation.

Thrombolytic Drugs

Alteplase

tissue plasminogen activator, tPA

- Mechanism of action: Alteplase has a low affinity for free plasminogen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug. Thus, alteplase is said to be fibrin selective, and at low doses, it has the advantage of lysing only fibrin, without unwanted degradation of other proteins-notably fibrinogen.
- This contrasts with streptokinase, which acts on free plasminogen and induces a general fibrinolytic state.
- Note: At dose levels of alteplase currently in use clinically, circulating plasminogen may be activated, resulting in hemorrhage.

Therapeutic uses:

- Alteplase is approved for the treatment of myocardial infarction, massive pulmonary embolism, and acute ischemic stroke.
- Alteplase seems to be superior to streptokinase in dissolving older clots and, ultimately, may be approved for other applications. Alteplase, administered within 3 hours of the onset of ischemic stroke, significantly improves clinical outcome-that is, the patient's ability to perform activities of daily living.
- Reteplase (Retavase) is similar to alteplase and can be used as an alternative.

Streptokinase

- **Mechanism of action:** Streptokinase has no enzymic activity. Instead, it forms an active one-to-one complex with plasminogen. This enzymatically active complex converts uncomplexed plasminogen to the active enzyme plasmin. In addition to the hydrolysis of fibrin plugs, the complex also catalyzes the degradation of fibrinogen as well as clotting Factors V and VII.

- **Therapeutic uses:** Streptokinase is approved for use in acute pulmonary embolism, deep-vein thrombosis, acute myocardial infarction, arterial thrombosis, and occluded access shunts.

Anistreplase
anisoylated plasminogen streptokinase activator complex

- Anistreplase is a preformed complex of streptokinase and plasminogen and it is considered to be a prodrug. Streptokinase must be released, and only plasminogen to which it was associated will get converted to plasmin.

Drugs Used to Treat 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, inhibit plasminogen activation, are orally active, and are excreted in the urine. A potential side effect of treatment is intravascular thrombosis.

B. Protamine sulfate

- Protamine sulfate antagonizes the anticoagulant effects of heparin. The positively charged protamine interacts with the negatively charged heparin, forming a stable complex without anticoagulant activity.

C. Vitamin K

- That vitamin K_1 (phytonadione) administration can stem bleeding problems due to the oral anticoagulants is not surprising, because those substances act by interfering with the action of the vitamin.
- The response to vitamin K is slow, requiring about 24 hours (time to synthesize new coagulation factors). Thus, if immediate hemostasis is required, fresh-frozen plasma should be infused.

D. Aprotinin

- Stops bleeding by blocking plasmin. It can inhibit streptokinase. It is approved for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass surgery.

Agents Used to Treat Anemia

A. Iron

- Supplementation with ferrous sulfate is required to correct the deficiency.
- Gastrointestinal disturbances caused by local irritation are the most common adverse effects of iron supplements.

B. Folic acid

- The primary use of folic acid is in treating deficiency states that arise from inadequate levels of the vitamin. Oral folic acid administered has no known toxicity.

C. Cyanocobalamin (vitamin B12)

- vitamin B_{12} supplementation is required in large oral doses, sublingually or once a month by the parenteral route.
- Therapy must be continued for the remainder of the life of a patient suffering from pernicious anemia.
- There are no known adverse effects of this vitamin.

D. Erythropoietin and darbepoetin

- Erythropoietin is a GP, normally made by the kidney, that regulates red blood cell proliferation and differentiation in bone marrow.
- Human erythropoietin, produced by recombinant DNA technology, is effective in the treatment of anemia caused by end-stage renal disease, anemia associated with human immunodeficiency virus infection, and anemia in some cancer patients.
- **Darbepoetin** is a long-acting version of erythropoietin that differs from erythropoietin by the addition of two carbohydrate chains, which improves its biologic activity. Therefore, darbepoetin has decreased clearance and has a half life about three times that of erythropoietin.
- Due to its delayed onset of action, darbepoetin has no value in acute treatment of anemia.
- Supplementation with iron may be required to assure an adequate response. The protein is usually administered intravenously in renal dialysis patients, but the subcutaneous route is preferred.

Agents Used to Treat Sickle-Cell Disease

- Clinical trials have shown that hydroxyurea can relieve the painful clinical course of sickle-cell disease.

- In sickle-cell disease, the drug apparently increases fetal hemoglobin levels, thus diluting the abnormal hemoglobin S (HbS).[9] This process takes several months. Polymerization of HbS is delayed in the treated patients so that painful crises are not caused by sickled cells blocking capillaries and causing tissue anoxia.

- Important side effects of hydroxyurea include bone marrow suppression and cutaneous vasculitis. It is important that hydroxyurea is administered under the supervision of a physician experienced in the treatment of sickle-cell disease.

End of Blood Drugs

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