***Lecture 5****.* ***Pharmacology of drugs affecting***

***the blood system***

**2. Pharmacology of drugs affecting platelet aggregation, coagulation, fybrinolysis – antiplatelet drugs, anticoagulants, fybrinolytics, antifybrinolytics, haemostatic drugs.**

This lecture describes drugs that are useful in the treatment of disorders of hemostasis. Thrombosis, the formation of an unwanted clot within a blood vessel, is the most common abnormality of hemostasis. Thrombotic disorders include acute myocardial infarction (MI), deep vein thrombosis (DVT), pulmonary embolism (PE), and acute ischemic stroke. These conditions are treated with drugs such as anticoagulants and fibrinolytics. Bleeding disorders related to the failure of hemostasis are less common than thromboembolic disorders. Bleeding disorders include hemophilia, which is treated with transfusion of recombinant factor VIII, and vitamin K deficiency, which is treated with vitamin K supplementation.

THROMBUS VERSUS EMBOLUS

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.

Physical trauma to the vascular system, such as a puncture or a cut, initi- ates a complex series of interactions between platelets, endothelial cells, and the coagulation cascade. These interactions lead to hemostasis or the cessation of blood loss from a damaged blood vessel. Platelets are central in this process. Initially, there is vasospasm of the damaged blood vessel to prevent further blood loss. The next step involves the formation of a platelet-fibrin plug at the site of the puncture. The creation of an unwanted thrombus involves many of the same steps as normal clot formation, except that the triggering stimulus is a pathologic condition in the vascular system, rather than external physical trauma.

Blood clotting factors are a group of substances found in blood plasma and platelets that provide blood clotting. Most clotting factors are proteins. Clotting factors also include calcium ions and some low molecular weight organic substances. Normally, protein coagulation factors are in the plasma in an inactive state.

If the factor is activated, then the letter “a” is added to its designation. The International Committee on Hemostasis and Thrombosis assigned Arabic numbering to platelet and Roman numbering to plasma factors. In total, 13 plasma factors and 22 platelet factors are isolated.

Coagulation factors are also found in other blood cells (erythrocytes and leukocytes), vascular endothelium and other tissues. They are sometimes isolated as independent groups (leukocyte, erythrocyte, tissue coagulation factors).

*Coagulation* is the process where blood loses its fluidity externally while still maintaining constant flow in the blood vessels. A series of steps leading to the formation of fibrin protein fibre involving different clotting factors. There are about thirteen known clotting factors:

* Fibrinogen (Factor 1)
* Prothrombin (Factor 2)
* Thromboplastin (Factor 3)
* Calcium (Factor 4)
* Proaccelerin or Labile Factor (Factor 5)
* Stable Factor (Factor 6) (*removed from classification)*
* Proconvertin (Factor 7)
* Antihemophilic Factor (Factor 8)
* Christmas Factor (Factor 9)
* Stuart - Power Factor (Factor 10)
* Plasma Thrombin antecedent (Factor 11)
* Hegman Factor (Factor 12)
* Fibrin Stabilising Factor (Factor 13)

These factors interact together to bring about coagulation cascade. These clotting factors are in an inactive state and must be activated to bring about blood clotting. Generally, the three stages involved in clotting formation are: formation of prothrombin activator, conversion of prothrombin into thrombin and finally thrombin is converted to fibrin. It is this fibrin produced that stabilizes the platelet plug which is called 'clot’. Upon repair of the vessel, the clot is eliminated and digested by an enzyme called plasmin. It is very important that the body regulates hemostasis properly as it can lead to thrombosis wherein excess and hemorrhage where there is little hemostasis.

PLATELET RESPONSE TO VASCULAR INJURY

Physical trauma to the vascular system, such as a puncture or a cut, initiates a complex series of interactions between platelets, endothelial cells, and the coagulation cascade. These interactions lead to hemostasis or the cessation of blood loss from a damaged blood vessel.

Platelets are central in this process. Initially, there is vasospasm of the damaged blood vessel to prevent further blood loss. The next step involves the formation of a platelet-fibrin plug at the site of the puncture. The creation of an unwanted thrombus involves many of the same steps as normal clot formation, except that the triggering stimulus is a pathologic condition in the vascular system, rather than external physical trauma.

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

Chemical mediators synthesized by endothelial cells: Prostacyclin is synthesized by intact endothelial cells and acts as an inhibitor of platelet aggregation. Prostacyclin {also known as prostaglandin 12) binds to platelet membrane receptors that are coupled to the synthesis of cyclic adenosine monophosphate {cAMP), an intracellular messenger.

Elevated levels of intracellular cAMP are associated with a decrease in intracellular calcium. Decreased intracellular calcium prevents 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 collagen in the subendothelial layers.

The corresponding platelet receptors are, thus, unoccupied, and as a result, platelet activation and aggregation are not initiated.

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.

*Formation of a clot*

Local stimulation of the coagulation cascade by tissue factors released from the injured tissue and by mediators on the surface of platelets results in the formation of thrombin {factor lla). In turn, thrombin, a serine protease, catalyzes the hydrolysis of fibrinogen to fibrin, which is incorporated into the clot. Subsequent cross-linking of the fibrin strands stabilizes the clot and forms a hemostatic platelet-fibrin plug.

*Fibrinolysis*

During clot 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

Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation. The platelet aggregation inhibitors described below inhibit cyclooxygenase-1 {COX-1), block GP II b/IIIa, or block ADP receptors, thereby interfering with the signals that promote platelet aggregation.

These agents are beneficial in the prevention and treatment of occlusive cardiovascular diseases, in the maintenance of vascular grafts and arterial patency, and as adjuncts to thrombin inhibitors or thrombolytic therapy in MI.

*Anticoagulants* are used for myocardial infarction, pulmonary infarction, thrombotic and embolic strokes, thrombophlebitis.

Applied prophylactically for atherosclerosis of the coronary arteries of cerebral vessels, rheumatic mitral heart disease.

In surgery, it is used to prevent the formation of blood clots in the postoperative period, during the hemodialysis procedure.

In hematology, it is used for use with automatic plasmapheresis devices for the preparation of human blood components (erythrocytes, platelets, plasma).

*Mechanism of action:*

**Heparin's anticoagulant** effect is binding to antithrombin Ill, with the rapid inactivation of coagulation factors.

Antithrombin Ill is an a globulin that inhibits serine proteases of thrombin (factor lla) and factor Xa.

In the absence of heparin, antithrombin Ill interacts very slowly with thrombin and factor Xa. When heparin molecules bind to antithrombin Ill, a conformational change occurs that catalyzes the inhibition of thrombin about 1000 times.

LMWHs complex with antithrombin Ill and inactivate factor Xa (including that located on platelet surfaces), but do not bind as avidly to thrombin.

*Therapeutic use:*

Heparin and the LMWHs are used for the treatment of acute venous thromboembolism. Heparin and LMWHs are also used for prophylaxis of postoperative venous thrombosis in patients undergoing surgery and those with acute MI.

These drugs are the anticoagulants of choice for treating pregnant women, because they do not cross the placenta, due to their large size and negative charge.

LMWHs do not require the same intense monitoring as heparin, thereby saving laboratory costs and nursing time. These advantages make LMWHs useful for both inpatient and outpatient therapy.

Pharmacokinetics:

Heparin must be administered subcutaneously or intravenously, because the drug does not readily cross membranes.

The LMWHs are usually administered subcutaneously. Heparin is often initiated as an intravenous to achieve immediate anticoagulation. This is followed by lower doses or continuous infusion of heparin. Anticoagulant effect with heparin occurs within minutes of IV administration (or 1 to 2 hours after subcutaneous injection), the maxmum anti-factor Xa activity of the LMWHs occurs about 4 hours after subcutaneous injection.

However, in renally impaired, pregnant, and obese patients, monitoring of factor Xa levels is recommended with LMWHs.

The inactive metabolites, as well as some of the parent heparin undergo renal excretion. The LMWHs are primarily eliminated in the urine.

Renal insufficiency prolongs the half-life of LMWH, and the dose of LMWH should be reduced in patients with renal impairment. The half-life of heparin is approximately 1.5 hours, whereas the half-life of the LMWHs is longer than that of heparin, ranging from 3 to 12 hours.

*Argatroban* is a synthetic parenteral anticoagulant that is derived from L-arginine. It is a direct thrombin inhibitor. *Argatroban* is used for the prophylaxis or treatment of venous thromboembolism in patients with HIT (Heparin‐induced thrombocytopenia). Anticoagulant effects are immediate. *Argatroban* is metabolized in the liver and has a half-life of about 39 to 51 minutes. As with other anticoagulants, the major side effect is bleeding.

*Bivalirudin* and *Desirudin* are parenteral anticoagulants that are analogs of hirudin, a thrombin inhibitor derived from saliva of the medicinal leech. These drugs are selective direct thrombin inhibitors that reversibly inhibit the catalytic site of both free and clot-bound thrombin.

*VITAMIN K ANTAGONISTS*

Coumarin anticoagulants have ability to antagonize the cofactor functions of vitamin K. Warfarin has a narrow therapeutic index. Therefore, frequent monitoring may be required.

**Warfarin.** *Mechanism of action:*

Factors II, VII, IX, and X require vitamin K as a cofactor for their synthesis by the liver.

The reduced vitamin K cofactor is converted to vitamin K epoxide during the reaction. Vitamin K is regenerated from the epoxide by vitamin K epoxide reductase, the enzyme that is inhibited by warfarin. Warfarin treatment results in the production of clotting factors with diminished activity (1 0% to 40% of normal).

Unlike heparin, the anticoagulant effects of watfarin are not observed immediately after drug administration.

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 use:*

*Warfarin* is used in the prevention and treatment of DVT (deep vein thrombosis) and PE (pulmonary embolism), stroke prevention, stroke prevention in the setting of atrial fibrillation and/or prosthetic heart valves, protein C and S deficiency, and antiphospholipid syndrome. It is also used for prevention of venous thromboembolism following orthopedic surgery.

*Pharmacokinetics:* Warfarin is rapidly absorbed after oral administration (100% bioavailability with little individual patient variation). Warfarin is highly bound to plasma albumin. Drugs that affect warfarin binding to plasma proteins can lead to variability in the therapeutic response to warfarin. Warfarin readily crosses the placental barrier. The mean half-life of warfarin is approximately 40 hours, but this value is highly variable among individuals. Warfarin is metabolized by the CYP450 system (mainly CYP2C9) to inactive components. After conjugation to glucuronic acid, the inactive metabolites are excreted in urine and feces. Agents that affect the metabolism of warfarin may alter its therapeutic effects. Warfarin has numerous drug interactions that may potentiate or attenuate its anticoagulant effect. The list of interacting drugs is extensive. A summary of some of the important interactions is shown in Figure

****

*Adverse effects:*

The principal adverse effect of *warfarin* is bleeding. Minor bleeding may be treated by withdrawal of the drug or administration of oral *vitamin K,* 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.* Skin lesions and necrosis are rare complications of *warfarin* therapy. Purple toe syndrome, a rare, painful, blue-tinged discoloration of the toe caused by cholesterol emboli from plaques, has also been observed with *warfarin* therapy.

*Warfarin* is teratogenic and is contraindicated in pregnancy.

***Dabigatran*** *–* DIRECT ORAL ANTICOAGULANTS

1. Mechanism of action: *Dabigatran etexilate* is the prodrug of the active moiety *dabigatran,* which is an oral direct thrombin inhibitor.
2. Therapeutic use: *Dabigatran* is approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It may also be used in the treatment of DVT and PE.
3. Pharmacokinetics: *Dabigatran etexilate* is administered orally. It is hydrolyzed to the active drug, *dabigatran,* by various plasma esterases. *Dabigatran* is metabolized by esterases. It is eliminated renally.
4. Adverse effects: The major adverse effect, like other anticoagulants, is bleeding. *Dabigatran* should be used with caution in renal impairment or in patients over the age of 75, as the risk of bleeding is higher in these groups.

Gl adverse effects: dyspepsia, abdominal pain, esophagitis, and Gl bleeding.

*Direct oral factor Xa inhibitors*

Mechanism of action: *Apixaban*, *betrixaban*, *edoxaban*, and *rivaroxaban* are oral inhibitors of factor Xa. Inhibition of factor Xa reduces the production of thrombin (lla) from prothrombin.

Therapeutic use: With the exception of *betrixaban,* these agents are approved for prevention of stroke in nonvalvular atrial fibrillation, as well as the treatment of DVT and PE. *Rivaroxaban* and *apixaban* are also used as prophylaxis to prevent or reduce the risk of recurrence of DVT and PE. *Betrixaban* is indicated for the prophylaxis of DVT and PE in hospitalized medical patients.

*PLATELET AGGREGATION INHIBITORS*

Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation. The platelet aggregation inhibitors inhibit cyclooxygenase-1 {COX-1), block ADP receptors, thereby interfering with the signals that promote platelet aggrgation.

These agents are beneficial in the prevention and treatment of occlusive cardiovascular diseases, in the maintenance of vascular grafts and arterial patency, and as adjuncts to thrombin inhibitors or thrombolytic therapy in MI.

***Aspirin***

Mechanism of action: Stimulation of platelets by thrombin, collagen, and ADP results in activation of platelet membrane phospholipases that liberate arachidonic acid from membrane phospholipids.

Arachidonic acid is first converted to prostaglandin H2 by COX-1. Prostaglandin H2 is further metabolized to thromboxane A2, which is released into plasma. Thromboxane A2 promotes the aggregation process that is essential for the rapid formation of a hemostatic plug. This shifts the balance of chemical mediators to favor the antiaggregatory effects of prostacyclin, thereby preventing platelet aggregation. The inhibitory effect is rapid, and aspirin-induced suppression of thromboxane A2 and the resulting suppression of platelet aggregation last for the life of the platelet, which is approximately 7 to 10 days. Repeated administration of *aspirin* has a cumulative effect on the function of platelets.

*Aspirin* is the only antiplatelet agent that irreversibly inhibits platelet function.

Therapeutic use: *Aspirin* is used in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent Ml, 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 antiplatelet dose of *aspirin* ranges from 50 to 325 mg daily.

*Pharmacokinetics:* When given orally, *aspirin* is absorbed by passive diffusion and quickly hydrolyzed to salicylic acid in the liver. Salicylic acid is further metabolized in the liver and some is excreted unchanged in the urine.

*Adverse effects:* Higher doses of *aspirin* increase drug-related toxicities as well as the probability that *aspirin* may also inhibit prostacyclin production.

*Adverse effects:*

Nonsteroidal anti-inflammatory drugs, such as ibuprofen, inhibit COX-1 by transiently competing at the catalytic site. Ibuprofen, if taken within the 2 hours prior to aspirin, can obstruct the access of aspirin to the serine residue and, thereby, antagonize platelet inhibition by aspirin. Therefore, immediate-release aspirin should be taken at least 60 minutes before or at least 8 hours after ibuprofen.

*P2Y12 ADP receptor antagonists*

*Ticlopidine, clopidogrel*, *prasugrel, ticagrelor*, and *cangrelor* are P2Y12 ADP receptor inhibitors that also block platelet aggregation but by a mechanism different from that of *aspirin.* All of these agents are administered orally, with the exception of *cangrelor,* which is an injectable formulation.

Mechanism of action: These drugs inhibit the binding of ADP to the P2Y12 receptor on platelets. *Ticagrelor* and *cangrelor* bind to the P2Y12 ADP receptor in a reversible manner. The other agents bind irreversibly.

The maximum inhibition of platelet aggregation is achieved in 2 minutes with intravenous (IV) *cangrelor,* 1 to 3 hours with *ticagrelor,* 2 to 4 hours with *prasugrel,* 3 to 4 days with *ticlopidine,* and 3 to 5 days with *clopidogrel.*

When treatment is suspended, the platelet system requires time to recover.

***Clopidogrel***is approved for prevention of atherosclerotic events in patients with a recent MI or stroke and in those with established peripheral arterial disease. It is also approved for prophylaxis of thrombotic events in acute coronary syndromes.

*Pharmacokinetics:* These agents require oral loading doses for quicker antiplatelet effect, except *cangrelor* that has a fast onset of action with intravenous administration.

After oral ingestion, the drugs are extensively bound to plasma proteins. They undergo hepatic metabolism by the cytochrome P-450 (CYP) system to active metabolites. Elimination of the drugs and metabolites occurs by both the renal and fecal routes.

*Pharmacokinetics:* *Clopidogrel* is a prodrug, and its therapeutic efficacy relies on its active metabolite, which is produced via metabolism by CYP 2C19.

Genetic polymorphism of CYP 2C19 leads to a reduced clinical response in patients who are "poor metabolizers" of *clopidogrel.* Tests are currently available to identify poor metabolizers, and it is recommended that other antiplatelet agents *(prasugrel* or *ticagrelor)* be prescribed for these patients. In addition, other drugs that inhibit CYP 2C19, such as *omeprazole* and *esomeprazole,*

*Adverse effects:* These agents can cause prolonged bleeding for which there is no antidote.

***Glycoprotein lIb/lIla inhibitors***

*Mechanism of action:* The GP lIb/lIla receptor plays a key role in stimulating platelet aggregation. A chimeric monoclonal antibody fragment, *abciximab*, inhibits the GP lIb/lIla receptor complex. By binding to GP lIb/lIla, *abciximab* blocks the binding of fibrinogen and von Willebrand factor and, consequently, aggregation does not occur. *Eptifibatide* and *tirofiban* act similarly to *abciximab,* by blocking the GP lIb/lIla receptor. *Eptifibatide* is a cyclic peptide that binds to GP lIb/lIla at the site that interacts with the arginine-glycine-aspartic acid sequence of fibrinogen. *Tirofiban* is not a peptide, but it blocks the same site as *eptifibatide.*

*Therapeutic use:* These agents are given intravenously, along with *heparin* and *aspirin,* as an adjunct to PCI (Percutaneous coronary intervention) for the prevention of cardiac ischemic complications. *Abciximab* is also approved for patients with unstable angina not responding to conventional medical therapy when PCI is planned within 24 hours.

*Pharmacokinetics:*

*Abciximab* is given by IV bolus, followed by IV infusion, achieving peak platelet inhibition within 30 minutes. The metabolism of *abciximab* is unknown. After cessation of *abciximab* infusion, platelet function gradually returns to normal, with the antiplatelet effect persisting for 24 to 48 hours. When IV infusion of *eptifibatide* or *tirofiban* is stopped, both agents are rapidly cleared from the plasma. *Eptifibatide* and its metabolites are excreted by the kidney. *Tirofiban* is excreted largely unchanged by the kidney and to a lesser extent in the feces.

Adverse effects: The major adverse effect of these agents is bleeding, especially if used with anticoagulants.

Pharmacological action of Apixaban (oral drug)

Direct acting anticoagulant, selective inhibitor of blood coagulation factor Xa.

The mechanism of action of apixaban is to inhibit the activity of blood coagulation factor Xa, reversibly and selectively blocking the active site of the enzyme. The presence of antithrombin III is not required to realize the antithrombotic effect of apixaban. Apixaban inhibits free and bound coagulation factor Xa, as well as prothrombinase activity. Apixaban has no direct effect on platelet aggregation, but indirectly inhibits thrombin-induced platelet aggregation. By inhibiting the activity of coagulation factor Xa, apixaban prevents the formation of thrombin and blood clots. Apixaban changes the values of indicators of the blood coagulation system: prolongs the prothrombin time, MHO and APTT.

*Pharmacokinetics*

After oral administration, apixaban is rapidly absorbed from the gastrointestinal tract. Cmax is achieved within 3-4 hours. The absolute bioavailability of apixaban reaches 50% when used in doses up to 10 mg. Eating does not affect the AUC or Cmax of apixaban. The pharmacokinetics of apixaban for doses up to 10 mg is linear. When taking apixaban in doses of more than 25 mg, there is a decrease in absorption, which is accompanied by a decrease in bioavailability. Metabolic parameters of apixaban are characterized by low or moderate inter- and intra-individual variability.

***THROMBOLYTIC DRUGS***

Acute thromboembolic disease in selected patients may be treated by the administration of drugs that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and, thus, dissolves clots.

*Common characteristics of thrombolytic agents*

*1. Mechanism of action:*Thethrombolyticagentsacteitherdirectlyor indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi. Clot dissolution and raperfusion occur with a higher frequency when therapy is initiated early after clot formation because clots become more resistant to lysis as they age. Unfortunately, increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregation and thrombosis. Strategies to prevent this include administration of antiplatelet drugs, such as *aspirin,* or antithrombotics such as *heparin.*

*2. Therapeutic use:* Originally used for the treatment of DVT and serious PE, thrombolytic drugs are currently used less frequently because of tendency to cause serious bleeding. For Ml, intracoronary delivery of the drugs is the most reliable in terms of achieving recanalization. However, cardiac catheterization may not be possible in the 2- to 6-hour "therapeutic window," beyond which significant myocardial salvage becomes less likely. Thus, thrombolytic agents are usually administered intravenously. Thrombolytic agents are helpful in restoring catheter and shunt function, by lysing clots causing occlusions. They are also used to dissolve clots that result in strokes.

*Adverse effects:* Thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug. Thus, hemorrhage is a major adverse effect. For example, a previously unsuspected lesion, such as a gastric ulcer, may hemorrhage following injection of a thrombolytic agent. These drugs are contraindicated in pregnancy and in patients with healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.

***Alteplase and tenecteplase***

*Alteplase*  (formerly known as *tissue plasminogen activator* or *tPA)* is a serine protease originally derived from cultured human melanoma cells. It is now obtained as a product of recombinant DNA technology. *Tenecteplase* is recombi- nant tPA with a longer half-life and greater binding affinity for fibrin than *alteplase. 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" at low doses. *Alteplase* is approved for the treatment of Ml, massive PE, and acute ischemic stroke. *Tenecteplase* is approved only for use in acute MI.

*Alteplase* has a very short half-life (5 to 30 minutes), and therefore, a portion of the total dose is injected intravenously as a bolus, and the remaining drug is administered over 1 to 3 hours, depending on the indication. *Tenecteplase* has a longer half-life and, therefore, may be administered as an intravenous bolus. *Alteplase* may cause angio- edema, and there may be an increased risk of this effect when com- bined with angiotensin-converting enzyme (ACE) inhibitors.

**DRUGS USED TO TREAT BLEEDING**

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 surgery. 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. Concentrated preparations of coagulation factors are available from human donors. However, these preparations carry the risk of transferring viral infections. Blood transfusion is also an option for treating severe hemorrhage.

***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.

***Protamine sulfate***

*Protamine sulfate* antagonizes the anticoagulant effects of *heparin.* This protein is derived from fish sperm or testes and is high in arginine content, which explains its basicity. The positively charged *protamine* interacts with the negatively charged *heparin,* forming a stable complex without anticoagulant activity. Adverse effects of drug administration include hypersensitivity as well as dys- pnea, flushing, bradycardia, and hypotension when rapidly injected.

***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. [Note: Intravenous *vitamin K* should be administered by slow IV infusion to minimize the risk of hypersensitivity or anaphylactoid reactions.] For the treatment of bleeding, the subcutaneous route of *vitamin K1* is less preferred, as it is not as effective as oral or IV administration. The response to *vitamin K1* is slow, requiring about 24 hours to reduce INA (time to synthesize new coagulation factors). Thus, if immediate hemostasis is required, fresh frozen plasma should be infused.

***ldarucizumab***

*ldarucizumab* is a monoclonal antibody fragment used to reverse bleeding caused by *dabigatran.* By binding to *dabigatran* and its metabolites, *idarucizumab* neutralizes anticoagulation. *ldarucizumab* is administered intravenously and is rapidly eliminated. *ldarucizumab* is used in emergency situations, in the inpa- tient setting. Because it reverses the effect of *dabigatran,* thrombosis is the most serious adverse effect of *idarucizumab.*