**LEC. 10 Pharmacology Dr. Ihab Alkhalifa**

**Anticoagulants and Antiplatelet Agents**

This chapter describes drugs that are useful in treating disorders of hemostasis, **Thrombosis** : is 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)
* Acute ischemic stroke.

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

**Bleeding disorders** involving the failure of hemostasis are less common

than thromboembolic diseases , include hemophilia which is treated with transfusion of recombinant factor VIII, and vitamin K deficiency, which is treated with vitamin K supplementation.

**Figure 22.1 summarizes the drugs used in treating dysfunctions of hemostasis.**

**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.

**Venous thrombosis**

 typically involves a clot that is rich in fibrin, with fewer platelets than are observed with arterial clots.



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**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.

**1- Vasospasm of the damaged blood vessel** to prevent further blood loss.

 **2- 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

**Resting non activated platelets**

Platelets act as vascular sentries, monitoring the integrity of the vascular endothelium ,  **Chemical mediators synthesized by endothelial cells**

such as **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), an intracellular messenger (Figure 22.2). Elevated levels of intracellular cAMP are associated with a decrease in intracellular calcium.

This prevents platelet activation and the subsequent release of platelet aggregation agents.

 **Damaged endothelial cells synthesize less prostacyclin than healthy cells, resulting in lower prostacyclin levels.** Since there is less prostacyclin to bind platelet receptors, less intracellular cAMP is synthesized, which leads to platelet aggregation.

**Roles of thrombin, thromboxanes, and collagen**: The platelet

membrane also contains receptors that can bind thrombin,

thromboxanes, and exposed collagen of the underlying connective tissue.

In the intact, normal vessel ,circulating levels of thrombin and thromboxane are low, and the intact endothelium covers the collagen in the subendothelial layers.

**When blood vessel injured & each of these receptor types occupied, triggers the platelets aggregation & adhesion.**

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**Steps of Platelet aggregation**

When platelets become activated and start to aggregate :

1) These actions are mediated by **several messenger systems** (ADP and serotonin) that ultimately result in elevated levels of calcium and a decreased concentration of cAMP within the platelet .

2) Activation of **thromboxane A2 synthesis.**

3) Activation of **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 .

**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 IIa).

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 ( Figure 22.2.



**Fibrinolysis**

During clot formation, the fibrinolytic pathway is locally activated Plasminogen is enzymatically processed to plasmin by plasminogen activators in the tissue (Figure 22.2).

Plasmin limits the growth of the clot and dissolves the fibrin network as wounds heal



**Drugs used for thrombotic diseases**

**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 (Figure 22.5).

The platelet aggregation inhibitors described below inhibit cyclooxygenase-1 (COX-1) or block GP IIb/IIIa or ADP receptors, thereby interfering with the signals that promote platelet aggregation Because these agents have different mechanisms of actions, synergistic or additive effects may be achieved when agents from different classes are combined.

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**

**A-Class** : Non-steroidal snit inflammatory drug (NSAIDs ) and Platelet aggregation inhibitors used for thrombosis

**B- Mechanism of action**:

**Aspirin** Inhibits thromboxane A2 synthesis by acetylation of a serine residue on the active site of Cyclooxygenase -1(COX-1 ) ( FIG. 22-7) which convert liberated arachidonic acid from membrane phospholipids (at the site of aggregation) , to prostacyclin by COX-1, **thereby aspirin irreversibly inactivating the enzyme** (Figure 22.6).resulting in suppression of platelet aggregation.

**C-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.

The half-life of aspirin ranges from 15 to 20 minutes and for salicylic acid is 3 to 12 hours.

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

**D-Therapeutic use**: Aspirin is used in :

* The prophylactic treatment of transient cerebral ischemia
* To reduce the incidence of recurrent MI
* To decrease mortality & prevention of MI.

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

Bleeding time is prolonged by aspirin treatment, causing complications that include an increased incidence of hemorrhagic stroke and gastrointestinal (GI) bleeding, especially at higher doses of the drug.

**Adenosin Di-phosphate (ADP) receptor inhibitors**

**Clopidogrel, Ticlopidine, and Ticagrelor**

**A-Class** : These drugs are : ADP receptor inhibitors that also block platelet aggregation but by a mechanism different from that of aspirin

**B-Mechanism of action**: These drugs inhibit the binding of ADP to its receptors on platelets and, thereby, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other (Figure 22.8) .

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When treatment is stopped , the platelet system requires time to recover

**D-Therapeutic use**: Clopidogrel is approved for :

* Prevention of atherosclerotic events in patients with a recent MI or stroke
* It is also approved for prophylaxis of acute coronary syndromes as unstable angina & MI).
* **Ticlopidine** is similar in structure to clopidogrel. It is indicated for the prevention of transient ischemic attacks (TIA) and strokes in patients with a prior cerebral thrombotic event.

However, due to life-threatening hematologic adverse reactions, ticlopidine is generally reserved for patients who are intolerant to other therapies.

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

These agents require loading doses for quicker antiplatelet effect. Food interferes with the absorption of ticlopidine but not with the other agents.

After oral ingestion, the drugs are extensively bound to plasma proteins. They undergo hepatic metabolism by the cytochrome P450 (CYP) system to active metabolites.

Elimination of the drugs and metabolites occurs by both the renal and fecal routes.

omeprazole and esomeprazole should not be administered concurrently with clopidogrel

**Adverse effects**: These agents can cause prolonged bleeding for which there is no antidote. Ticlopidine is associated with severe hematologic reactions that limit its use, such as agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia.

Clopidogrel causes fewer adverse reactions, and the incidence of neutropenia is lower. However, TTP has been reported as an adverse effect for both clopidogrel and prasugrel

**Note/ Additionally, ticagrelor carries a black box warning for diminished effectiveness with concomitant use of aspirin doses above 100 mg.**

**The GP IIb/IIIa receptor inhibitors**

* **Abciximab, Eptifibatide, and Tirofiban**
1. **Class** : The GP IIb/IIIa receptor blockers , used for thrombotic diseases therapy .
2. **Mechanism of action:** The GP IIb/IIIa receptor plays a key role in stimulating platelet aggregation. Its monoclonal antibody abciximab [ab-SIKS-eh-mab], inhibits the GP IIb/IIIa receptor complex. By binding to GP IIb/IIIa, abciximab blocks the binding of fibrinogen cloting factor and, consequently, aggregation does not occur (Figure 22.9).



Eptifibatide [ep-ti-FIB-ih-tide] and tirofiban [tye-roe-FYE-ban] act similarly to abciximab, by blocking the GP IIb/IIIa receptor.

Eptifibatide is a cyclic peptide that binds to GP IIb/IIIa 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

1. **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 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 in the feces.

**D-Therapeutic use**: These agents are given intravenously, along with heparin and aspirin, as an adjunct to PCI 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.

**Adverse effects**: The major adverse effect of these agents is bleeding especially if used with anticoagulants. Figure 22.10 summarizes the effects of the GP IIb/IIIa receptor antagonists on mortality and MI.

**Phosphodiesterase inhibitors**

* **Dipyridamole**

**A-Class :** phosphodiesterase inhibitors, cAMP agonist used for thrombotic diseases therapy

**thereby resulting in decreased thromboxane A2 synthesis.**

**B- Mechanism of action** : Dipyridamole [dye-peer-ID-a-mole], a coronary vasodilator, increases intracellular levels of cAMP by inhibiting cyclic nucleotide phosphodiesterase thereby resulting in decreased thromboxane A2 synthesis.

The drug may potentiate the effect of prostacyclin to antagonize platelet stickiness and, therefore, decrease platelet adhesion to thrombogenic surfaces (Figure 22.2).

**C-Pharmacokinetics** : Dipyridamole has variable bioavailability following oral administration. It is highly protein bound .

The drug undergoes hepatic metabolism, as well as glucuronidationand is excreted mainly in the feces. Patients with unstable angina should not use dipyridamole because of its vasodilating properties, which may worsen ischemia (coronary steal phenomenon).

**D-Theraputic uses** : Dipyridamole is used for stroke prevention and is usually given in combination with aspirin.

Adverse effects : Dipyridamole commonly causes headache and can lead to orthostatic hypotension (especially if administered IV.

**NORMAL BLOOD COAGULATION STEPS**

**1- thrombin formation** : The coagulation process that generates thrombin consists of two interrelated pathways, the extrinsic and the intrinsic systems.

**The extrinsic system** is initiated by the activation of clotting factor VII by tissue factor ( thromboplastin ) in response to vascular injury, tissue factor becomes exposed to blood. There it can bind and activate factor VII, initiating the extrinsic pathway.

**The intrinsic system** is triggered by the activation of clotting factor XII. This occurs when blood comes into contact with the collagen in the damaged wall of a blood vessel.

**2- Formation of fibrin**

Both the extrinsic and the intrinsic systems lead to factor Xa is produced, which **converts prothrombin (factor II) to thrombin (factor IIa), ( Figure 32.13).**

Thrombin plays a key role in coagulation, because it is responsible for generation of fibrin, which forms the mesh-like matrix of the blood clot.

**If thrombin is not formed or if its function is impeded (for example, by antithrombin III), coagulation is inhibited.**

Note : Latin numbers = I=1 , II=2 , III=3, IV= 4, V=5 , V1= 6, VII =7 , VIII= 8 , IX= 9

 X= 10 , XI= 11, XII= 12

 factor II = prothrombin , factor IIa = thrombin

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**ANTICOAGULANT Drugs**

The anticoagulant drugs inhibit either :

A- the action of the coagulation factors : heparin

 B- interfere with the vitamin K dependent synthesis of the coagulation factors

(coumarins coumponds as warfarin which work as vit K antagonists

**Heparin and low molecular weight heparins**

**A-class :** Heparin is natural glycosaminoglycan Anticoagulant used for thrombotic diseases therapy

Heparin classes or types :

**1- Unfractionated heparin of different molecular weight**

**2- Low molecular weight heparin ( LMWHs)**

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

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

It is extracted for commercial use from porcine intestinal mucosa.

**1- Unfractionated heparin** : is naturally occurring anticoagulant as a macromolecule complexed with histamine in mast cells, that is a mixture of sulfated polysaccharides with molecular weights averaging 15,000–18,000.

Heparin is extracted for commercial use from porcine intestinal mucosa. And used as an injectable, rapidly acting anticoagulant that is often used acutely to interfere with the formation of thrombi

**Antithrombin III** is an α globulin that inhibits factor IIa and factor Xa

**راجع الشكل السابق**(Figure 32.13).

When heparin molecules bind to antithrombin III, a conformational change occurs that catalyzes the **inhibition of thrombin about 1000-fold** Figure 22.12).

**B-** **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** (thrombin (factor II) & Xa ) (Figure 22.12).



**C-Pharmacokinetics :** Heparin must be administered subcutaneously or intravenously, because the drug does not readily cross membranes (Figure 22.14).

Heparin is often initiated as an intravenous bolus to achieve immediate anticoagulation. This is followed by lower doses or continuous infusion of heparin, titrating the dose so that the activated partial thromboplastin time (aPTT) is 1.5- to 2.5-fold that of the normal control.

**[Note: The aPTT is the standard test used to monitor the extent of anticoagulation with heparin.]**

Whereas the anticoagulant effect with heparin occurs within minutes of IV administration (or 1 to 2 hours after subcutaneous injection.

In the blood, heparin binds to many proteins that neutralize its activity, causing unpredictable pharmacokinetics.

Heparin binding to plasma proteins is variable in patients with thromboembolic diseases. Although generally restricted to the circulation, heparin is taken up by the monocyte/macrophage system, and it undergoes depolymerization and desulfation to inactive products.

**The inactive metabolites of heparin are excreted into the urine.**

**Renal insufficiency prolongs the half-life of heparin . Therefore, the dose should be reduced in patients with renal impairment.**

The half-life of heparin is approximately 1.5 hours.

**Adverse effects of heparin**

* Immune-mediated reactions and carries a risk of venous and arterial embolism.
* Heparin therapy should be discontinued when patients show severe thrombocytopenia.
* osteoporosis has been observed in patients on long-term heparin therapy.

**Low molecular weight forms of heparin ( LMWHs)**

**Enoxaparin, Dalteparin and Tinzaparin**

**A-Class** : low molecular weight forms of heparin ( LMWHs) about one-third the size of unfractionated heparin, can also act as anticoagulants produced by enzymatic depolymerization of unfractionated heparin.

**B-Mechanism of action for LMWHs** : these drugs complex with antithrombin III and **inactivate factor Xa** (including that located on platelet surfaces) but do not bind as avidly to thrombin. (Figure 22.1)

**C- Pharmacokinetics :**  The maximum activity of the LMWHs occurs about 4 hours after subcutaneous injection.

**The LMWHs are administered subcutaneously.**

It is usually not necessary to monitor coagulation values with LMWHs

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 LMWHs, are excreted into the urine.

Renal insufficiency prolongs the half-life of LMWHs. Therefore, the dose of LMWHs should be reduced in patients with renal impairment.

The half-life of LMWHs is longer than that of heparin, ranging from 3 to 12 hours **.**

**D-Therapeutic use For heparin & LMWHs:**

Heparin and the LMWHs limit the expansion of thrombi by preventing fibrin formation. These agents are used for :

1- Treatment of acute venous thromboembolism (DVT or PE).

2- Postoperative venous thrombosis in patients undergoing surgery (for example hip replacement)

3- Patients with acute MI.

4- 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..

**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.

Possible adverse reactions include chills, fever, urticaria, and anaphylactic shock. Heparin-induced thrombocytopenia (HIT) is a serious condition, in which circulating Heparin and LMWH are mostly con­ned to the vascular system.

**Contraindications**

Heparin and LMWHs are contraindicated in patients who have hypersensitivity to heparin, bleeding disorders, alcoholism, or who have had recent surgery of the brain, eye, or spinal cord.

**Q/ what are advantages make LMWHs useful for both inpatient and outpatient therapy ?**

A / Since LMWHs do not require the same intense monitoring as heparin the chief complication of heparin and LMWH therapy is bleeding , Careful monitoring of the patient and laboratory parameters is required to minimize bleeding, thereby using LMWH therapy saving laboratory costs and nursing time.

Excessive bleeding may be managed by discontinuing the drug or by treating with protamine sulfate, When infused slowly, protamine sulfate combines ionically with heparin to form a stable, inactive complex.

It is very important that the dosage of protamine sulfate is carefully titrated (1 mg for every 100 units of heparin administered because protamine sulfate is a weak anticoagulant, and excess amounts may trigger bleeding episodes or worsen bleeding potential.

**Coumarin drugs : 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 [WAR-far-in]. 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 warfarin therapy is monitored. The INR corrects for variations that occur with different thromboplastin reagents used to perform testing at various institutions.

The goal of warfarin therapy is an INR of 2 to 3 for most indications, with an INR of 2.5 to 3.5 targeted for some mechanical valves and other indications.

Warfarin has a narrow therapeutic index. Therefore, it is important that the INR is maintained within the optimal range as much as possible, and frequent monitoring may be required

 **B- Mechanism of action:** warfarin inhibits activation of vit-K dependent Factors ( II, VII, IX, and X ) require vitamin K as a cofactor for their synthesis by the liver. Activated factors , bind calcium ions, which are essential for interaction between the coagulation factors and platelet membranes leading to clotting blood .

vitamin K cofactor is converted to vitamin K epoxide during the activation 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 (10% to 40% of normal

**C-Pharmacokinetics :**

* Warfarin is rapidly absorbed after oral administration 100% bioavailability with little individual patient variation..
* Warfarin is highly bound to plasma albumin, which prevents its diffusion into the cerebrospinal fluid, urine, and breast milk.
* Drugs that affect warfarin binding to plasma proteins can lead to variability in the therapeutic response to warfarin. drugs that have a greater affinity for the albumin-binding site, such as sulfonamides, can displace the anticoagulant and lead to a transient, elevated activity.
* Warfarin readily crosses the placental barrier. The mean half-life of warfarin is approximately 40 hours,
* Warfarin is metabolized by the CYP450 system 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 as fluconazole, metronidazole & sulfonamides ( inhibits warfarine metabolism & increase its action )

While barbiturate, rifampicin stimulates warfarin metabolism and reduce its anticoagulant action.

**Note/ Unlike heparin, the anticoagulant effects of warfarin are not observed immediately** after drug administration. Instead, peak effects may be delayed for 72 to 96 hours, which is the time required to deplete the pool of circulating clotting factors.

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

1. **Therapeutic use & Adverse effects** : Warfarin is used :
2. in the prevention and treatment of DVT and PE, stroke in the setting of atrial fibrillation and/or prosthetic heart valves
3. It is also used for prevention of venous thromboembolism during orthopedic or gynecologic surgery.

**Adverse effects**: The principal adverse effect of warfarin is hemorrhage and the agent

 1-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.

2-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.

3- Warfarin is teratogenic and should never be used during pregnancy. If anticoagulant therapy is needed during pregnancy heparin or LMWH may be administered.

**THROMBOLYTIC DRUGS**

Acute thromboembolic disease in selected patients may be treated by the administration of agents that activate the conversion of plasminogen to plasmin, a protease that hydrolyzes fibrin and, thus, dissolves clots (Figure 22.18).

**1-Streptokinase**, one of the first such agents to be approved, causes a systemic fibrinolytic state that can lead to bleeding problems.

**2-Alteplase acts** more locally on the thrombotic fibrin to produce fibrinolysis.

**3-Urokinase** is produced naturally in human kidneys and directly converts plasminogen into active plasmin.

Figure 22.19 compares the thrombolytic agents.

**Mechanism of action**: The thrombolytic agents share some common features. All act either directly or indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi (Figure 22.18).

**Therapeutic use:** Originally used for the treatment of DVT and serious PE, thrombolytic drugs are now being used less frequently for these conditions.

thrombolytic agents are usually administered intravenously

**Adverse effects:** The thrombolytic agents show an unwanted hemorrhage as a major side effect

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 .



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**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 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 (Figure 22.23).

* **Aminocaproic acid and Tranexamic acid**

Fibrinolytic states can be controlled by the administration of aminocaproic [a-mee-noe-ka-PROE-ic] acid or tranexamic [tran-ex-AM-ic] 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 [PROE-ta-meen] sulfate antagonizes the anticoagulant effects of heparin forming a stable complex without anticoagulant activity.

**Adverse effects** of drug administration include hypersensitivity as well as dyspnea 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 not 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 INR (time to synthesize new coagulation factors).

Thus, if immediate hemostasis is required fresh frozen plasma should be infused .