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.

PLATELET INHIBITORS
Abciximab REOPRO
Aspirin VARIOUS
Cilostazol PLETAL
Clopidogrel PLAVIX
Dipyridamole PERSANTINE
Eptifibatide INTEGRILIN
Prasugrel EFFIENT
Ticagrelor BRILINTA
Ticlopidine TICLID
Tirofiban AGGRASTAT
ANTICOAGULANTS
Apixaban ELIQUIS
Argatroban ARGATROBAN
Bivalirudin ANGIOMAX
Dabigatran PRADAXA
Dalteparin FRAGMIN
Desirudin IPRIVASK
Enoxaparin LOVENOX
Fondaparinux ARIXTRA
Heparin
Rivaroxaban XARELTO
Tinzaparin INNOHEP
Warfarin COUMADIN, JANTOVEN
THROMBOLYTIC AGENTS
Alteplase (tPA) ACTIVASE
Reteplase RETAVASE
Streptokinase
Tenecteplase TNKASE
Urokinase KINLYTIC
TREATMENT OF BLEEDING
Aminocaproic acid AMICAR
Protamine sulfate
Tranexamic acid CYKLOKAPRON, LYSTEDA
Vitamin K_1 (phytonadione) MEPHYTON

Figure 22.1
Summary of drugs used in treating dysfunctions of hemostasis.

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Drugs used for thrombotic diseases

PLATELET AGGREGATION INHIBITORS

❖ Aspirin

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.

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

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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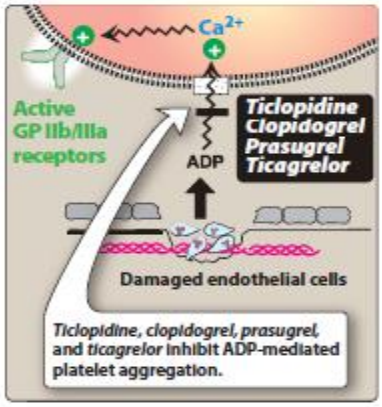

Figure 22.8
Mechanism of action of *ticlopidine, clopidogral prasugrel*, and *ticagrelor*. GP = glycoprotein.

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.

The GP IIb/IIIa receptor inhibitors

❖ Abciximab, Eptifibatide, and Tirofiban

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

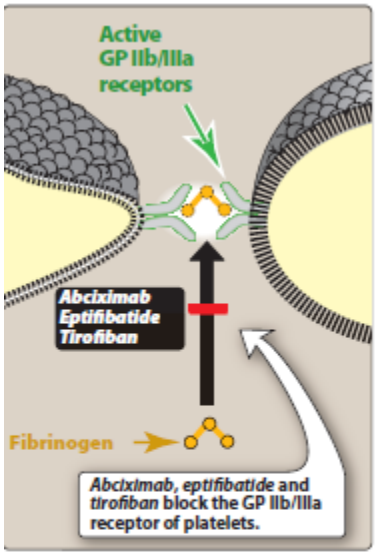

Figure 22.9
Mechanism of action of glycoprotein (GP) IIb/IIIa receptor blockers.

Phosphodiesterase inhibitors

❖ Dipyridamole

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).

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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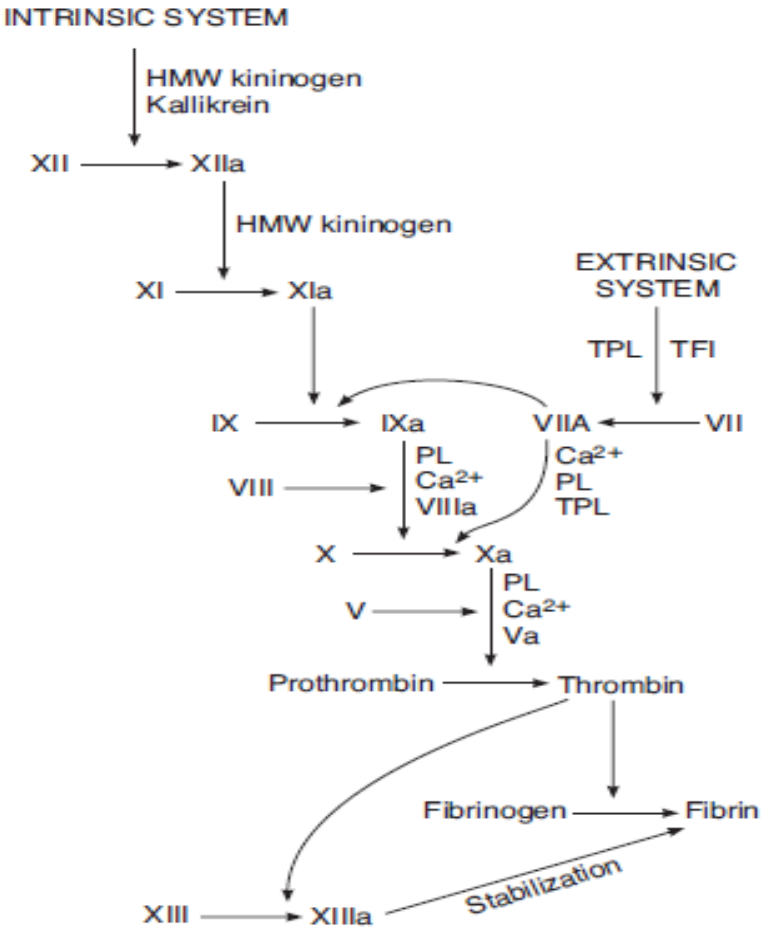

FIGURE 32–13 **The clotting mechanism.** a, active form of clotting factor. TPL, tissue thromboplastin; TFI, tissue factor pathway inhibitor. For other abbreviations, see Table 32–5.

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ANTICOAGULANT Drugs

The anticoagulant drugs inhibit either the action of the coagulation factors for example, heparin) or interfere with the synthesis of the coagulation factors (for example, vitamin K antagonists such as warfarin

Heparin and low molecular weight heparins

Unfractionated heparin is a mixture of straight-chain, anionic glycosaminoglycans with a wide range of molecular weights.

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** (IIa thrombin & Xa) (Figure 22.12).

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.

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.

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.

for most indications, with an INR of ٢The goal of warfarin therapy is an INR of 2 to 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

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 .

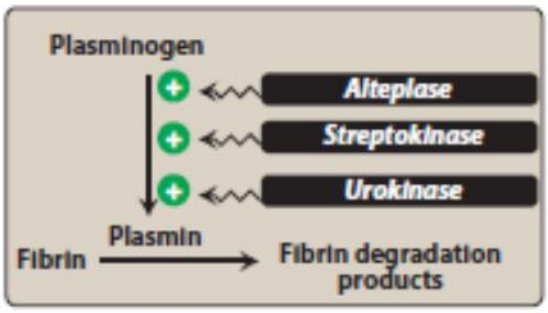

Figure 22.18
Activation of plasminogen by thrombolytic drugs.

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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 .