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Anticoagulant, Antiplatelet, and Fibrinolytic (Thrombolytic) Drugs

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Little intravascular coagulation of blood occurs in normal physiological conditions. Hemostasis involves the interplay of three procoagulant phases (*vascular, platelet,* and *coagulation*) that promote blood clotting to prevent blood loss (Fig. 22.1). The fibrinolytic system prevents propagation of clotting beyond the site of vascular injury and is involved in clot dissolution, or *lysis* (Fig. 22.2).

HEMOSTATIC MECHANISMS

Endothelial cells maintain a nonthrombogenic lining in blood vessels. This results from several phenomena, including (1) the maintenance of a transmural negative electrical charge, which is important in preventing adhesion of circulating platelets; (2) the release of plasminogen activators, which activate the fibrinolytic pathway; (3) the activation of protein C, which degrades
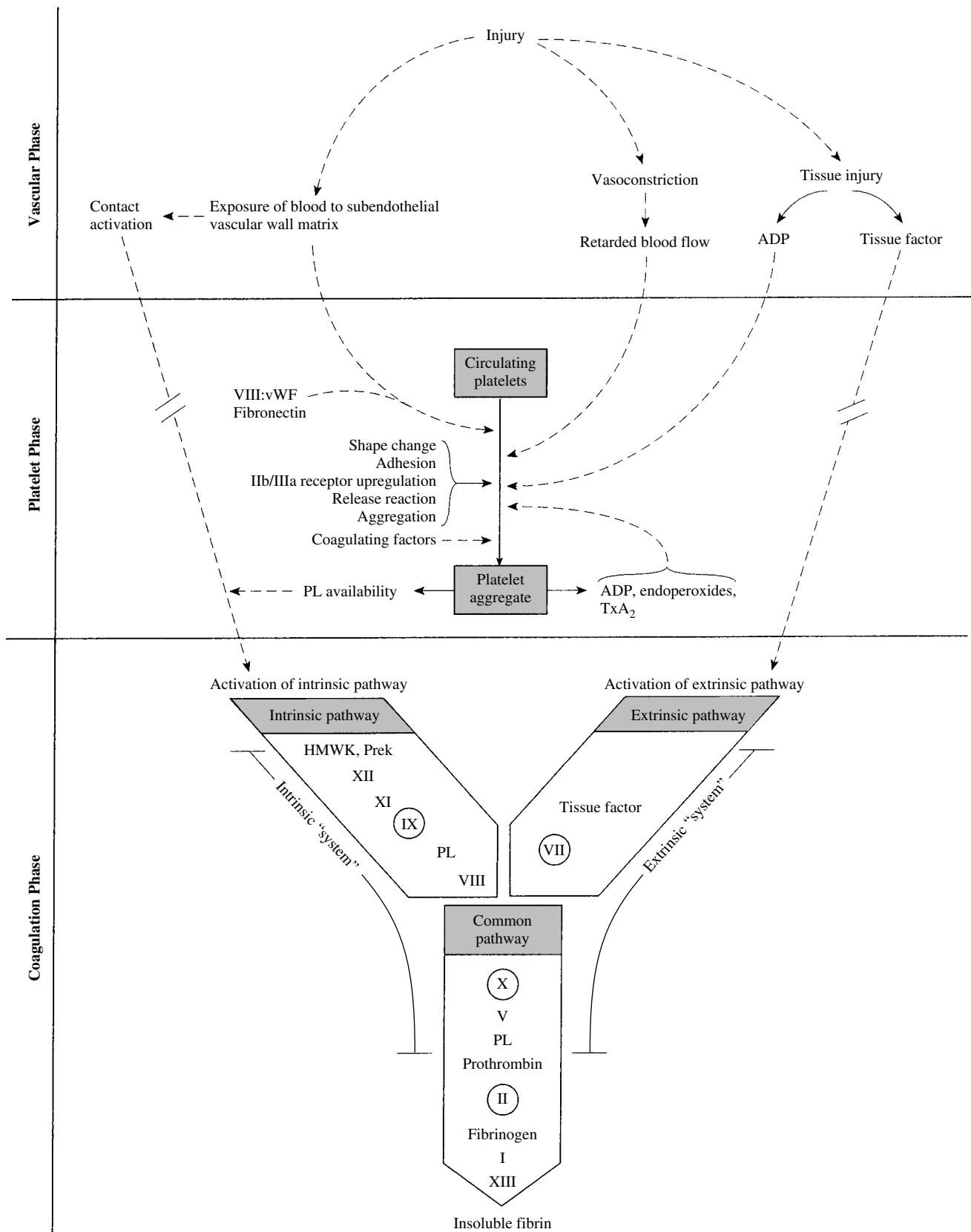
FIGURE 22.1

Hemostatic mechanisms showing the relationships among the vascular, platelet, and coagulation phases. Action is denoted by broken arrows, transformation by solid arrows. Circled factors are those that require vitamin K for activity. Proteins C and S, which degrade factors Va and VIIIa and require vitamin K for activity, are not shown. This figure is a highly simplified summary; see supplemental reading for further details. PL, platelet phospholipid; HMWK, high molecular weight kininogen; PreK, prekallikrein; ADP, adenosine diphosphate; vWF, Von Willebrand factor; TxA_2, thromboxane A_2. (Modified with permission from Wintrobe MM et al. Clinical Hematology (7th ed.). Philadelphia: Lea & Febiger, 1974:390, 422.)
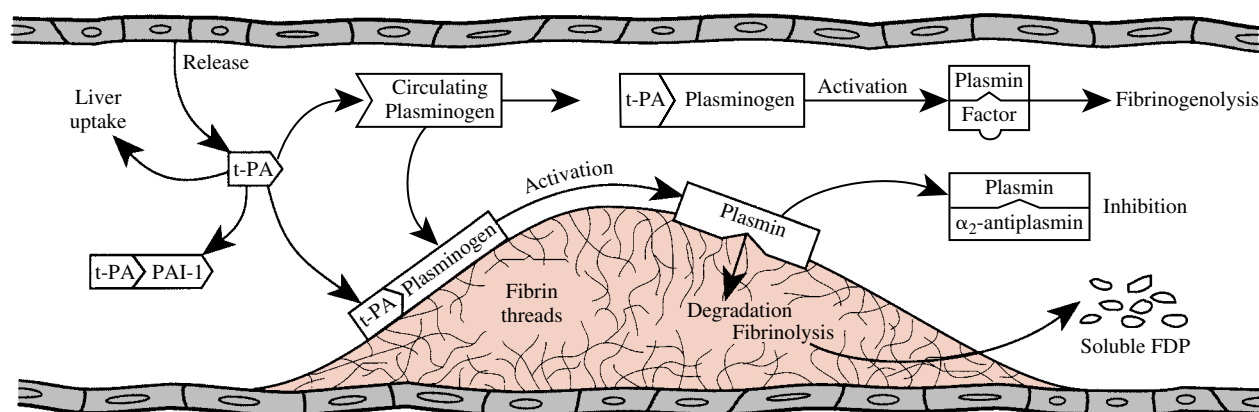
FIGURE 22.2

The fibrinolytic system in blood vessels showing the physiological mechanisms of activation of plasminogen on fibrin to cause fibrinolysis and the pathophysiological mechanism in the blood to cause fibrinogenolysis. The release of t-PA from vascular endothelium and the inhibitory effect of α_2-antiplasmin on plasmin activity are depicted. PAI-1, plasminogen activator inhibitor-1; FDP, fibrin degradation products; factor, coagulation factor. (Modified with permission from Wiman B and Hamsten A. The fibrinolytic enzyme system and its role in the etiology of thromboembolic disease. Semin Thromb Hemost 1990;16:207.)

coagulation factors, a process involving thrombin and its endothelial cofactor (thrombomodulin); (4) the production of heparinlike proteoglycans, which inhibit coagulation; and (5) the release of prostacyclin (PGI$_2$), a potent inhibitor of platelet aggregation.

In normal individuals, injury severe enough to cause hemorrhage initiates coagulation. Vasoconstriction, combined with increased tissue pressure caused by extravasated blood, results in a reduction, or stasis, of blood flow. Stasis favors the restriction of thrombus formation to the site of injury. The extravasation of blood exposes platelets and the plasma clotting factors to subendothelial collagen and endothelial basement membranes, which result in activation of the clotting sequence. Several substances that participate in coagulation are released or become exposed to blood at the site of injury. These include adenosine diphosphate (ADP), a potent stimulus to platelet aggregation, and *tissue factor,* a membrane glycoprotein cofactor of factor VII.

Platelet aggregation is the most important defense mechanism against leakage of blood from the circulation. Ordinarily, unstimulated platelets do not adhere to the endothelial cell surface. Following disruption of the endothelial lining and exposure of blood to the subendothelial vessel wall, platelets come into contact with and adhere within seconds to factor VIII:vWF polymers and fibronectin. The platelets change shape and then undergo a complex secretory process termed the *release reaction.* This results in the release of ADP from platelet granules and activation of platelet phospholipase A$_2$. This enzyme, cyclooxygenase, and thrombox-

ane synthetase sequentially convert arachidonic acid into cyclic endoperoxides and thromboxane A$_2$ (TxA$_2$). In contrast to endothelial cells, platelets lack PGI$_2$ synthetase. Upon platelet activation with mediators of aggregation (ADP, serotonin, TxA$_2$, epinephrine, thrombin, collagen, platelet activating factor), the integrin platelet receptor for plasma fibrinogen, glycoprotein IIb/IIa (GPIIb/IIa), is expressed. The arginine–glycine–aspartic acid (RDG) tripeptide in the α-chain of fibrinogen mediates binding of fibrinogen to the GPIIb/IIIa complex. Fibrinogen, forming a bridge between platelets, and the binding of fibrinogen and Von Willebrand's factor to activated platelets via GPIIb/IIIa are key events in platelet–platelet interactions and play a major role in thrombus formation. Aggregation of circulating platelets to those already adherent amplifies the release reaction.

Other substances liberated from platelets during the release reaction include serotonin (which may promote vasospasm in coronary vessels), platelet factor 4 (a basic glycoprotein that can neutralize the anticoagulant action of circulating heparin), platelet-derived growth factor (a mitogen that initiates smooth muscle cell proliferation and may be involved in atherogenesis), and factors that are also found in the plasma (factor V, factor VIII:vWF, and fibrinogen). During aggregation, the rearrangement of the platelet membrane makes available a phospholipid surface (*platelet factor 3*) that along with Ca^{++} is required for the activation of several clotting factors. *The platelet aggregate becomes a hemostatic plug and is the structural foundation for the assembly of the fibrin network.*

COAGULATION SYSTEMS

Two interrelated processes, the *intrinsic* and *extrinsic* coagulation systems (Fig. 22.1), converge on a common pathway that leads to the activation of factor X, the formation of thrombin (factor IIa), and the conversion by thrombin of the soluble plasma protein fibrinogen into insoluble fibrin. The extrinsic pathway appears to be important for initiating fibrin formation, while the intrinsic pathway is involved in fibrin growth and maintenance; both systems constitute the coagulation cascade. This series of linked and overlapping reactions involves conversion of proenzymes (designated by roman numerals) into serine proteases (designated by roman numeral followed by the suffix -a), and cofactors that speed the protease reactions (factors Va and VIIa).

Exposure of blood to tissue factors activates the extrinsic system, beginning with the proteolytic conversion of factor VII into factor VIIa. Degradation of factors V and VIII:C by protein C at locations distant from the site of vascular injury aids in the localization of clot formation. The coagulation cascade is capable of tremendous amplification as the protease reactions progress. Many of the activated coagulation factors feed back positively in the extrinsic, intrinsic, and common pathways and accelerate the reactions. Either deficiency in a single clotting factor or therapy with the drugs described in this chapter will result in abnormal hemostasis.

ANTICOAGULANT DRUGS

Anticoagulant drugs inhibit the development and enlargement of clots by actions on the coagulation phase. They do not lyse clots or affect the fibrinolytic pathways.

Heparin

Two types of heparin are used clinically. The first and older of the two, standard (unfractionated) heparin, is an animal extract. The second and newer type, called low-molecular-weight heparin (LMWH), is derived from unfractionated heparin. The two classes are similar but not identical in their actions and pharmacokinetic characteristics.

Standard (Unfractionated) Heparin

Heparin (*heparin sodium*) is a mixture of highly electronegative acidic mucopolysaccharides that contain numerous *N*- and *O*-sulfate linkages. It is produced by and can be released from mast cells and is abundant in liver, lungs, and intestines.

Mechanism of Action

The anticoagulation action of heparin depends on the presence of a specific *ser*ine *p*rotease *in*hibitor (serpin) of thrombin, antithrombin III, in normal blood.

Heparin binds to antithrombin III and induces a conformational change that accelerates the interaction of antithrombin III with the coagulation factors. Heparin also catalyzes the inhibition of thrombin by heparin cofactor II, a circulating inhibitor. Smaller amounts of heparin are needed to prevent the formation of free thrombin than are needed to inhibit the protease activity of clot-bound thrombin. Inhibition of free thrombin is the basis of low-dose prophylactic therapy.

Absorption, Metabolism, and Excretion

Heparin is prescribed on a unit (IU) rather than milligram basis. The dose must be determined on an individual basis. Heparin is not absorbed after oral administration and therefore must be given parenterally. *Intravenous administration results in an almost immediate anticoagulant effect.* There is an approximate 2-hour delay in onset of drug action after subcutaneous administration. Intramuscular injection of heparin is to be avoided because of unpredictable absorption rates, local bleeding, and irritation. Heparin is not bound to plasma proteins or secreted into breast milk, and it does not cross the placenta.

Heparin's action is terminated by uptake and metabolism by the reticuloendothelial system and liver and by renal excretion of the unchanged drug and its depolymerized and desulfated metabolite. The relative proportion of administered drug that is excreted as unchanged heparin increases as the dose increases. Renal insufficiency reduces the rate of heparin clearance from the blood.

Pharmacological Actions

The physiological function of heparin is not completely understood. It is found only in trace amounts in normal circulating blood. It exerts an antilipemic effect by releasing lipoprotein lipase from endothelial cells; heparinlike proteoglycans produced by endothelial cells have anticoagulant activity. Heparin decreases platelet and inflammatory cell adhesiveness to endothelial cells, reduces the release of platelet-derived growth factor, inhibits tumor cell metastasis, and exerts an antiproliferative effect on several types of smooth muscle.

Therapy with heparin occurs in an inpatient setting. *Heparin inhibits both in vitro and in vivo clotting of blood.* Whole blood clotting time and activated partial thromboplastin time (aPTT) are prolonged in proportion to blood heparin concentrations.

Adverse Effects

The major adverse reaction resulting from heparin therapy is hemorrhage. Bleeding can occur in the urinary or gastrointestinal tract and in the adrenal gland. Subdural hematoma, acute hemorrhagic pancreatitis, hemarthrosis, and wound ecchymosis also occur. The incidence of life-threatening hemorrhage is low but

variable. Heparin-induced thrombocytopenia of immediate and delayed onset may occur in 3 to 30% of patients. The immediate type is transient and may not involve platelet destruction, while the delayed reaction involves the production of heparin-dependent antiplatelet antibodies and the clearance of platelets from the blood. Heparin-associated thrombocytopenia may be associated with irreversible aggregation of platelets (white clot syndrome). Additional untoward effects of heparin treatment include hypersensitivity reactions (e.g., rash, urticaria, pruritus), fever, alopecia, hypoaldosteronism, osteoporosis, and osteoalgia.

Contraindications, Cautions, and Drug Interactions

Absolute contraindications include serious or active bleeding; intracranial bleeding; recent brain, spinal cord, or eye surgery; severe liver or kidney disease; dissecting aortic aneurysm; and malignant hypertension. Relative contraindications include active gastrointestinal hemorrhage, recent stroke or major surgery, severe hypertension, bacterial endocarditis, threatened abortion, and severe renal or hepatic failure.

Drugs that inhibit platelet function (e.g., aspirin) or produce thrombocytopenia increase the risk of bleeding when heparin is administered. *Oral anticoagulants and heparin produce synergistic effects.* Many basic drugs precipitate in the presence of the highly acidic heparin (e.g., antihistamines, quinidine, quinine, phenothiazines, tetracycline, gentamicin, neomycin).

Heparin Antagonist

The specific heparin antagonist protamine can be employed to neutralize heparin in cases of serious hemorrhage. Protamines are basic low-molecular-weight, positively charged proteins that have a high affinity for the negatively charged heparin molecules. The binding of protamine to heparin is immediate and results in the formation of an inert complex. Protamine has weak anticoagulant activity.

Low-Molecular-Weight Heparin

Low-molecular-weight fragments produced by chemical depolymerization and extraction of standard heparin consist of heterogeneous polysaccharide chains of molecular weight 2,000 to 9,000. The LMWH molecules contain the pentasaccharide sequence necessary for binding to antithrombin III but not the 18-saccharide sequence needed for binding to thrombin. Compared to standard heparin, LMWH has a 2- to 4-fold greater antifactor Xa activity than antithrombin activity.

LMWH has greater bioavailability than standard heparin, a longer-lasting effect, and dose-independent clearance pharmacokinetics. The predictable relationship between anticoagulant response and dose allows anticoagulant control without laboratory tests. LMWH is more effective than standard heparin in preventing and treating venous thromboembolism. The incidence of thrombocytopenia after administration of LMWH is lower than with standard heparin. Adverse drug reactions like those caused by standard heparin have been seen during therapy with LMWH, and overdose is treated with protamine.

LMWH is available for subcutaneous administration as enoxaparin (*Lovenox*), dalteparin (*Fragmin*), ardeparin (*Normiflo*), and tinzaparin (*Innohep*). Danaparoid (*Orgaran*), a heparinoid composed of heparin sulfate, dermatan sulfate, and chondroitin sulfate, has greater factor Xa specificity than LMWH. Bleeding due to danaparoid is not reversed by protamine.

Orally Effective Anticoagulants

The orally effective anticoagulant drugs are fat-soluble derivatives of 4-hydroxycoumarin or indan-1,3-dione, and they resemble vitamin K. *Warfarin is the oral anticoagulant of choice.* The indandione anticoagulants have greater toxicity than the coumarin drugs.

Mechanism of Action

Unlike heparin, *the oral anticoagulants induce hypocoagulability only in vivo.* They are vitamin K antagonists. Vitamin K is required to catalyze the conversion of the precursors of vitamin K–dependent clotting factors II, VII, IX, and X. This involves the posttranslational γ-carboxylation of glutamic acid residues at the *N*-terminal end of the proteins. The γ-carboxylation step is linked to a cycle of enzyme reactions involving the active hydroquinone form of vitamin K (K_1H_2). The regeneration of K_1H_1 by an epoxide reductase is blocked by the oral anticoagulants. *These drugs thus cause hypocoagulability by inducing the formation of structurally incomplete clotting factors.*

Commercial warfarin is a racemic mixture of S- and R-enantiomers; S-warfarin is more potent than R-warfarin.

Absorption, Metabolism, and Excretion

Warfarin is rapidly and almost completely absorbed after oral administration and is bound extensively (>95%) to plasma proteins. Since it is the unbound drug that produces the anticoagulant effect, displacement of albumin-bound warfarin by other agents may result in bleeding. Although these drugs do not cross the blood-brain barrier, they can cross the placenta and may cause teratogenicity and hemorrhage in the fetus.

Warfarin is inactivated by hepatic P450 isozymes; hydroxylated metabolites are excreted into the bile and then into the intestine. Hepatic disease may potentiate the anticoagulant response.

Pharmacological Actions

Warfarin is used both on an inpatient and outpatient basis when long-term anticoagulant therapy is indicated. The onset of anticoagulation is delayed, the latency being determined in part by the time required for absorption and in part by the half-lives of the vitamin K–dependent hemostatic proteins. *The anticoagulant effect will not be evident in coagulation tests such as prothrombin time until the normal factors already present in the blood are catabolized;* this takes 5 hours for factor VII and 2 to 3 days for prothrombin (factor II). The anticoagulant effect may be preceded by a transient period of hypercoagulability due to a rapid decrease in protein C levels. More rapid anticoagulation is provided, when necessary, by administering heparin.

Warfarin is administered in conventional doses or minidoses to reduce bleeding. The dose range is adjusted to provide the desired end point.

Adverse Effects

The principal adverse reaction to warfarin is hemorrhage. Prolonged therapy with the coumarin-type anticoagulants is relatively free of untoward effects. Bleeding may be observable (e.g., skin, mucous membranes) or occult (e.g., gastrointestinal, renal, cerebral, hepatic, uterine, or pulmonary). Rarer untoward effects include diarrhea, small intestine necrosis, urticaria, alopecia, skin necrosis, purple toes, and dermatitis.

Contraindications, Cautions, and Drug Interactions

Oral anticoagulants are ordinarily contraindicated in the presence of active or past gastrointestinal ulceration; thrombocytopenia; hepatic or renal disease; malignant hypertension; recent brain, eye, or spinal cord surgery; bacterial endocarditis; chronic alcoholism; and pregnancy. These agents also should not be prescribed for individuals with physically hazardous occupations.

Minor hemorrhage caused by oral anticoagulant overdosage can be treated by discontinuing drug administration. Oral or parenteral vitamin K_1 (phytonadione) administration will return prothrombin time to normal by 24 hours. This period is required for de novo synthesis of biologically active coagulation factors. *Serious hemorrhage may be stopped by administration of fresh frozen plasma or plasma concentrates containing vitamin K–dependent factors.*

Dietary intake of vitamin K and prior or concomitant therapy with a large number of pharmacologically unrelated drugs can potentiate or inhibit the actions of oral anticoagulants. Laxatives and mineral oil may reduce the absorption of warfarin. The patient's prothrombin time and international normalized ratio (INR) should be monitored when a drug is added or removed from therapy. Selected drug interactions involving oral anticoagulants are summarized in Table 22.1.

TABLE 22.1   Drug Interactions Involving Oral Anticoagulants

Drugs That Increase Oral Anticoagulant Effects

Acetaminophen	Chloral hydrate	Fenoprofen	Lovastatin	Propranolol
Alcohol (acute intoxication)	Chlorpropamide	Fluconazole	Mefenamic acid	Quinidine, quinine
Allopurinol	Chymotrypsin	Fluoroquinolones	Metronidazole	Ranitidine
Amiodarone	Cimetidine	Fluoxetine	Micolazole	Sulfamethoxazole-trimethoprim
Anabolic and androgenic steroids	Clarithromycin	Fluvastatin	Nabumetone	Sulfinpyrazone
Aspirin	Clofibrate	Gemcitabine	Nalidixic acid	Sulindac
Azapropazone	Cotrimoxazole	Gemfibrozil	Naproxen	Tamoxifen
Bromelains	Dextran	Glucagon	Omeprazole	Ticlopidine
Cephalosporins	Diazoxide	Heparin	Oral hypoglycemics	Tolmetin
Carboplatin/Etoposide	Diflunisal	Ibuprofen	Pentoxifylline	Tolterodine
Celecoxib	Disulfiram	Indomethacin	Phenylbutazone	Tricyclic antidepressants
Chenodiol	Ethacrynic acid	Inhalation anesthetics	Phenytoin	Troglitazone
	Felbamate	Isoniazid	Piroxicam	Vitamin E
	Fenofibrate	Levamisole/Fluorouracil	Propafenone	

Drugs That Decrease Oral Coagulant Effects

Alcohol (chronic abuse)	Barbiturates	Dextrothyroxine	Nafcillin	Sucralfate
Aminoglutethimide	Carbamazepine	Ginseng	Oral contraceptives	Trazodone
Antacids	Chlordiazepoxide	Griseofulvin	Penicillins (large doses)	Vitamin K (large doses)
Antihistamines	Cholestyramine	Haloperidol	Primidone	
Azathioprine	Corticosteroids	Meprobamate	Rifampin	

Oral anticoagulants also may potentiate hypoglycemia caused by oral hypoglycemic agents, and may enhance phenytoin toxicity.

Direct Thrombin Inhibitor Anticoagulants

Two drugs that are direct inhibitors of thrombin but that do not involve antithrombin III or vitamin K in their mechanism of action have been approved to provide intravenous anticoagulation in patients with heparin-induced thrombocytopenia. Lepirudin (*Refludan*) and bivalirudin (*Angiomax*), which are analogues of the leech peptide anticoagulant hirudin, bind in a 1:1 complex with thrombin to inhibit its protease activity. Argatroban (*Acova, Novastan*), a synthetic analogue of arginine, interacts reversibly with and inhibits thrombin's catalytic site. Both drugs have a short half-life. Lipuridin is cleared following metabolism and urinary excretion of changed and unchanged drug; hepatic metabolism of argatroban is a therapeutic advantage in patients with renal insufficiency. No antagonists for these drugs are available.

CLINICAL INDICATIONS FOR ANTICOAGULANT THERAPY

Anticoagulant therapy provides prophylactic treatment of venous and arterial thromboembolic disorders. *Anticoagulant drugs are ineffective against already formed thrombi,* although they may prevent their further propagation. Generally accepted major indications for anticoagulant therapy with heparin and warfarin include the following:

Deep Vein Thrombosis

Venous stasis resulting from prolonged bed rest, cardiac failure, or pelvic, abdominal, or hip surgery may precipitate thrombus formation in the deep veins of the leg or calf and may lead to fatal pulmonary embolism. Heparin may also be used prophylactically following surgery.

Arterial Embolism

Since arterial emboli formation involves platelet aggregation and leukocyte and erythrocyte infiltration into the fibrin network, the treatment and prophylaxis of arterial thrombi are more difficult. Arterial embolism is treated more successfully with heparin than with the oral anticoagulants. Anticoagulants are useful for prevention of systemic emboli resulting from valvular disease (rheumatic heart disease) and from valve replacement.

Atrial Fibrillation

Restoration of sinus rhythm in atrial fibrillation may dislodge thrombi that have developed as a result of stasis in the enlarged left atrium. The risk of stroke and systemic arterial embolism is decreased by anticoagulation in such patients.

Unstable Angina and Myocardial Infarction

In patients with unstable angina and severe ischemia requiring hospital admission, therapeutic doses of heparin along with antiplatelet therapy (discussed later) are thought to provide additive protection of the patient against myocardial reinfarction. *Thrombolytic drugs are more effective than anticoagulants in treating coronary thromboembolism and in establishing reperfusion of occluded arteries after an infarction.* Anticoagulants in combination with antiplatelet drugs reduce the incidence of thrombus formation and reocclusion after coronary arterial bypass surgery and percutaneous coronary angioplasty.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation is characterized by widespread systemic activation of the coagulation system, consumption of coagulation factors, occlusion of small vessels by a coat of fibrin, and a hypocoagulation state with bleeding. In conjunction with management of the underlying factor or factors leading to the disorder and coagulation factor and platelet replacement, bleeding may be managed with intravenous (IV) heparin, LMWH, and antithrombin III (*Thrombate*).

ANTIPLATELET DRUGS

The formation of platelet aggregates and thrombi in arterial blood may precipitate coronary vasospasm and occlusion, myocardial infarction, and stroke and contribute to atherosclerotic plaque development. *Drugs that inhibit platelet function are administered for the relatively specific prophylaxis of arterial thrombosis and for the prophylaxis and therapeutic management of myocardial infarction and stroke.* After an infarction or stroke, antiplatelet therapy must be initiated within 2 hours to obtain significant benefit. The antiplatelet drugs are administered as adjuncts to thrombolytic therapy, along with heparin, to maintain perfusion and to limit the size of the myocardial infarction. Recently, antiplatelet drugs have found new importance in preventing thrombosis in percutaneous coronary intervention procedures (angioplasty and stent). Administration of an antiplatelet drug increases the risk of bleeding.

Aspirin inhibits platelet aggregation and prolongs bleeding time. It is useful for preventing coronary thrombosis in patients with unstable angina, as an adjunct to thrombolytic therapy, and in reducing recurrence of thrombotic stroke. It acetylates and irreversibly inhibits cyclooxygenase (primarily cyclooxygenase-1) both in platelets, preventing the formation of TxA_2, and in endothelial cells, inhibiting the synthesis of PGI_2 (see

Chapter 26). While endothelial cells can synthesize cyclooxygenase, platelets cannot. *The goal of therapy with aspirin is to selectively inhibit the synthesis of platelet TxA$_2$ and thereby inhibit platelet aggregation.* This is accomplished with a low dose of aspirin (160 to 325 mg per day), which spares the endothelial synthesis of PGI$_2$. If ibuprofen is taken concurrently, it will bind reversibly to cyclooxygenase and prevent the access of aspirin to its acetylation site and thus antagonize the ability of aspirin to inhibit platelets. Dipyridamole (*Persantine*), a coronary vasodilator, is a phosphodiesterase inhibitor that increases platelet cyclic adenosine monophosphate (cAMP) concentrations. It also may potentiate the effect of PGI$_2$, which stimulates platelet adenylate cyclase. However, dipyridamole itself has little effect on platelets in vivo. Dipyridamole in combination with warfarin is beneficial in patients with artificial heart valves; it is also useful in combination with aspirin (*Aggrenox*) for the secondary prevention of stroke.

Ticlopidine (*Ticlid*) and clopidogrel (*Plavix*) are structurally related drugs that irreversibly inhibit platelet activation by blocking specific purinergic receptors for ADP on the platelet membrane. This action inhibits ADP-induced expression of platelet membrane GPIIb/IIIa and fibrinogen binding to activated platelets. Ticlopidine and clopidogrel are useful antithrombotic drugs. Oral ticlopidine is indicated for prevention of thrombotic stroke in patients who cannot tolerate aspirin and for patients who have had thrombotic stroke. Inhibition of ADP-induced platelet aggregation occurs within 4 days, and the full effect requires approximately 10 days. Ticlopidine is taken with food, is well absorbed, binds extensively to plasma proteins, and is metabolized by the liver. Gastrointestinal disturbances, neutropenia, and agranulocytosis have been observed. Clopidogrel produces fewer side effects than ticlopidine.

Pharmacological agents, such as abciximab (*ReoPro*), eptifibatide (*Integrillin*), and tirofiban (*Aggrastat*), that interrupt the interaction of fibrinogen and Von Willebrand's factor with the platelet GPIIb/IIIa complex are capable of inhibiting aggregation of platelets activated by a wide variety of stimuli. These drugs are given intravenously. The chimeric monoclonal antibody abciximab binds to the GPIIb/IIIa complex, preventing interactions of fibrinogen and Von Willebrand's factor with the integrin receptor. Abciximab is used in conjunction with angioplasty and stent procedures and is an adjunct to fibrinolytic therapy (discussed later). Patients who have murine protein hypersensitivity or who have received abciximab previously may produce an immune response after second administration. Eptifibatide, a cyclic peptide, and tirofiban, a small nonpeptide molecule, both bind reversibly to the GPIIb/IIIa complex and competitively prevent the interaction of the clotting factors with this receptor.

FIBRINOLYTIC SYSTEM

The fibrinolytic system (Fig. 22.2) is involved in restricting clot propagation in the blood and in the removal of fibrin as wounds heal. Treatment of patients with fibrinolytic (thrombolytic) drugs that activate the fibrinolytic system is not a substitute for the anticoagulant drugs. *The purpose of thrombolytic therapy is rapid lysis of already formed clots.*

Fibrinolysis is initiated by the activation of the proenzyme *plasminogen* (present in clots and in plasma) into plasmin, a protease enzyme not normally present in blood. Plasmin catalyzes the degradation of fibrin. The conversion of plasminogen to plasmin is initiated normally by the plasminogen activators, tissue-type plasminogen activator (t-PA) and single-chain urokinase-type plasminogen activator (scu-PA). t-PA and scu-PA are serine protease enzymes synthesized by the endothelium and released into the circulation. The endothelium also releases plasminogen activator inhibitor-1 (PAI-1), which complexes with and inactivates t-PA in the plasma.

t-PA and scu-PA bind with high affinity to fibrin on the clot surface. Circulating plasminogen binds to the plasminogen activator–fibrin complex to form a ternary complex consisting of fibrin, activator, and plasminogen. Therefore, the specificity of t-PA and scu-PA binding to fibrin normally localizes plasmin protease activity to thrombi.

Circulating plasmin is rapidly neutralized by α_2-antiplasmin, a physiological serine protease inhibitor that forms an inert complex with plasmin. In contrast, fibrin-bound plasmin is resistant to inactivation by α_2-antiplasmin. Under normal circumstances plasma t-PA is inactive because it is inhibited by PAI-1, while t-PA that is bound to fibrin is unaffected by PAI-1. In addition, plasma t-PA has a very rapid turnover in blood (half-life 5 to 8 minutes). For these reasons, fibrinolysis is normally restricted to the thrombus.

Activation of the fibrinolytic system with thrombolytic drugs can disturb the balance of these regulatory mechanisms and elevate circulating plasmin activity. Plasmin has low substrate specificity and degrades fibrinogen (fibrinogenolysis), plasminogen, and coagulation factors. The systemic unphysiological activation of the fibrinolytic system with thrombolytic drugs causes consumption of the coagulation factors, a lytic state, and bleeding.

Thrombolytic (Fibrinolytic) Drugs

Thrombolytic drugs cause lysis of formed clots in both arteries and veins and reestablish tissue perfusion.

Mechanism of Action

Thrombolytic drugs are plasminogen activators. The ideal thrombolytic agent is one that can be administered

intravenously to produce clot-selective fibrinolysis without activating plasminogen to plasmin in plasma. Older (first generation) thrombolytic agents are not clot selective, and appreciable systemic fibrinogenolysis accompanies successful clot lysis. Newer (second generation) thrombolytic agents bind to fibrin and activate fibrinolysis more than fibrinogenolysis. Third-generation agents have improved fibrin specificity and pharmacokinetic properties.

Pharmacological Actions and Clinical Uses

Thrombolytic drugs are indicated for the management of severe pulmonary embolism, deep vein thrombosis, and arterial thromboembolism and are especially important therapy after myocardial infarction and acute ischemic stroke. Thrombolysis must be accomplished quickly after myocardial or cerebral infarction, since clots become more difficult to lyse as they age. Recanalization after approximately 6 hours provides diminishing benefit to the infarcted area. The incidence of rethrombosis and reinfarction is greater when thrombolytic drugs with shorter plasma half-lives are used. Concurrent administration with heparin followed by warfarin, as well as antiplatelet drugs, is advocated to reduce reocclusion. Adjunctive anticoagulant and antiplatelet drugs may contribute to bleeding during thrombolytic therapy.

Adverse Effects

The principal adverse effect associated with thrombolytic therapy is bleeding due to fibrinogenolysis or fibrinolysis at the site of vascular injury. Hypofibrinogenemia may occur and should be monitored with laboratory tests. At effective thrombolytic doses, the second- and third-generation agents cause less extensive fibrinogenolysis, but bleeding occurs with a similar incidence for all agents. Life-threatening intracranial bleeding may necessitate stoppage of therapy, administration of whole blood, platelets or fresh frozen plasma, protamine (if heparin is present), and an antifibrinolytic drug (discussed later).

Contraindications

The contraindications to the use of thrombolytic drugs are similar to those for the anticoagulant drugs. Absolute contraindications include active bleeding, cardiopulmonary resuscitation (trauma to thorax is possible), intracranial trauma, vascular disease, and cancer. Relative contraindications include uncontrolled hypertension, earlier central nervous system surgery, and any known bleeding risk.

First-Generation Thrombolytic Drugs

Streptokinase (*Streptase, Kabikinase*), a nonenzymatic protein from Lancefield group C β-hemolytic strepto-

cocci, is an *indirectly acting* activator of plasminogen. It forms a 1:1 complex with plasminogen, which results in a conformational change and exposure of an active site that can convert additional plasminogen into plasmin. The systemic administration of streptokinase can produce significant lysis of acute deep vein and pulmonary emboli and acute arterial thrombi. Intravenous or intracoronary artery (IC) streptokinase is effective in establishing recanalization after myocardial infarction and in increasing short-term survival. The greatest benefit of streptokinase appears to be achieved by early intravenous drug administration. Complications associated with the administration of streptokinase include hemorrhage, pyrexia, and allergic or anaphylactic reactions. Patients may be refractory to streptokinase during therapy because of preexisting or streptokinase-induced antibodies. Streptokinase has two half-lives. The faster one (11 to 13 minutes) is due to drug distribution and inhibition by circulating antibodies, and the slower one (23 to 29 minutes) is due to loss of enzyme activity.

Urokinase (*Abbokinase*) is a two-polypeptide chain serine protease that does not bind avidly to fibrin and that directly activates both circulating and fibrin-bound plasminogen. The plasma half-life of urokinase is approximately 10 to 20 minutes. Urokinase is derived from human cells and thus is not antigenic. Urokinase produces a significant resolution of recent pulmonary emboli.

Second- and Third-generation Thrombolytic Drugs

The principal physiological activator of plasminogen in the blood, tissue-type plasminogen activator (t-PA, alteplase) (*Activase*), has a high binding affinity for fibrin and produces, after IV administration, a fibrin-selective activation of plasminogen. This selectivity is not absolute; circulating plasminogen also may be activated by large doses or lengthy treatment. After intravenous administration, alteplase is more efficacious than streptokinase in establishing coronary reperfusion. At equieffective thrombolytic doses, alteplase causes less fibrinogenolysis than streptokinase, but bleeding occurs with a similar incidence. The rate of rethrombosis after t-PA is greater than after streptokinase, possibly because alteplase is rapidly cleared from the blood (half-life is 5 to 10 minutes), and several administrations may be warranted. Reocclusion may be lessened by administration of heparin and antiplatelet drugs. Alteplase is a product of recombinant DNA technology and consists predominantly of the single-chain form (recombinant human tissue-type plasminogen activator, rt-PA). Upon exposure to fibrin, rt-PA is converted to the two-chain dimer.

Two genetically engineered variants of human t-PA have better pharmacological properties than alteplase. Reteplase (*Retavase*) contains only the peptide domains required for fibrin binding and protease activity. These

changes increase potency and speed the onset of action. Reteplase may penetrate further into the fibrin clot than alteplase. The half-life of the drug remains short, however. Tenecteplase (TNK-tPA) (*TNKase*) has a longer half-life than alteplase, binds more avidly to fibrin, and in contrast to many other thrombolytic agents, may be administered as an IV bolus.

Anistreplase (*Eminase*) consists of streptokinase in a noncovalent 1:1 complex with plasminogen. Anistreplase is catalytically inert because of acylation of the catalytic site of plasminogen. However, the affinity of plasminogen binding to fibrin is maintained. It has a long catalytic half-life (90 minutes), and the time required for nonenzymatic deacylation lengthens its thrombolytic effect after IV injection. Anistreplase is more effective than streptokinase in establishing coronary reperfusion, but it causes considerable fibrinogenolysis and is antigenic.

Antifibrinolytic Drugs

Hyperplasminemia resulting from thrombolytic therapy exposes fibrinogen and other coagulation factors, plasminogen, and α_2-antiplasmin to nonspecific proteolysis by plasmin, a process normally regulated by α_2-antiplasmin. Consumption of these factors and extensive fibrin dissolution leads to hemorrhage. The binding of plasminogen to fibrin involves interactions with lysine-binding sites in plasminogen. These interactions are blocked by antifibrinolytic drugs such as aminocaproic acid (*Amicar*) and tranexamic acid (*Cyklokapron*); plasminogen activation primarily and plasmin proteolytic activity are inhibited.

In addition to being an *antidote to fibrinogenolysis* during thrombolytic therapy, antifibrinolytic drugs are used orally and intravenously to control bleeding following surgery. They also are useful adjuncts to coagulation factor replacement during dental surgery in hemophiliac patients. Antifibrinolytic drugs are contraindicated if intravascular coagulation is present. These drugs *may* cause nausea.

Agents for Controlling Blood Loss

Cardiopulmonary bypass, with extracorporeal circulation during cardiac artery bypass graft or heart valve replacement surgery, causes transient hemostatic defects in blood cells and perioperative bleeding. The protease inhibitor aprotinin (*Trasylol*) inhibits kallikrein (coagulation phase) and plasmin (fibrinolysis) and protects platelets from mechanical injury. The overall effect after infusion is a decrease in bleeding.

Several biological agents are used intravenously to maintain coagulability in the face of factor deficiencies in hemophilia or Von Willebrand's disease patients. Manufacture of these substances involves extraction from human blood or recombinant technology. They include antihemophilic factor (factor VIII) (*Alphanate, Bioclate,* others) for hemophilia A patients, factor IX concentrate (*Bebulin, AlphaNine, Mononine,* others) for hemophilia B patients, and factor VIIa (*NovoSeven*) for hemophilia and Von Willebrand patients. An increase in factor VIII levels by desmopressin (*DDAVP, Concentraid,* others), an analog of vasopressin, is useful for managing bleeding in hemophilia A and mild Von Willebrand's disease patients. Anti-inhibitor coagulant complex (*Autoplex, FEIBA*) provides activated vitamin K–dependent clotting factors to return coagulability to the blood in hemophilia patients and other patients with acquired inhibitors to clotting factors.

Study Questions

1. Which of the following statements describe why warfarin is not used to prevent blood coagulation in blood collection devices used at blood donating centers?
   (A) Warfarin does not bind to plastic tubing or glass.
   (B) The anticoagulant effect of warfarin occurs only in vivo.
   (C) Warfarin is a prodrug, which must be activated in the liver into the active compound.
   (D) The gastric enzymes needed to convert R-warfarin into S-warfarin are unstable near plastic.
   (E) Warfarin is chemically unstable and is degraded unless made fresh and used immediately.
2. All of the following statements about warfarin are true EXCEPT which one?
   (A) An adverse drug reaction may occur if warfarin is displaced from plasma protein binding sites.
   (B) Warfarin crosses the placenta.
   (C) Drugs that are metabolized by the liver can alter the anticoagulant effect of warfarin.
   (D) Warfarin is eliminated from the body unchanged in the urine.
   (E) Warfarin is a vitamin K antagonist.
3. Which of the following is an adverse effect associated with pharmacotherapy using heparin?
   (A) An increase in the number of circulating platelets
   (B) Thrombocytopenia
   (C) Purple toe syndrome
   (D) Teratogenicity to the fetus
   (E) An increase in the circulating level of antithrombin III
4. Which of the following is a drug that blocks the ADP receptor on the antiplatelet membrane?
   (A) Aspirin
   (B) Abciximab
   (C) Dipyridamole
   (D) Clopidogrel
   (E) Eptifibatide
5. The thrombolytic drug reteplase is improved over older drugs like streptokinase in what respect?
   (A) Reteplase may be taken orally.
   (B) Reteplase is antigenic.
   (C) Reteplase binds to fibrin.
   (D) Bleeding does not occur with reteplase.
   (E) Reteplase produces less thrombocytopenia.

ANSWERS

1. **B.** Warfarin does not produce an anticoagulant effect in vitro. It inhibits coagulation of blood only in vivo, because the effect depends upon warfarin's effect in the liver on the production of clotting factors. Warfarin does not require conversion into an active drug. It inhibits the post-ribosomal carboxylation of glutamic acid residues in the vitamin K-dependent clotting factors. Therefore, heparin rather than warfarin is used when blood is collected from donors and stored.
2. **D.** Warfarin is metabolized in the liver by P450 enzyme system and is appreciably metabolized before it is eliminated. Adverse drug reactions are seen in patients taking warfarin if a second drug displaces warfarin from its protein binding sites in the blood or induces or inhibits the hepatic P450 system. Warfarin can cross the placenta and exert anticoagulant and other effects in the fetus at normal doses given to the mother.
3. **B.** Thrombocytopenia is a frequent side effect association with heparin. This reduction in the level of circulating platelets increases bleeding. Purple toes are encountered during warfarin therapy. Heparin may be administered to pregnant mothers without risk to the fetus. Heparin requires antithrombin III for its anticoagulant action, but does not increase the level of this protein in the blood.
4. **C.** Aspirin inhibits platelet cyclooxygenase. Abciximab, a monoclonal antibody, binds to and inhibits the platelet glycoprotein IIb/IIIa receptor. Dipyridamole inhibits platelet cyclic AMP phosphodiesterase and raises cyclic AMP levels. Eptifibatide binds to the glycoprotein IIb/IIIa complex.
5. **C.** Reteplase binds to fibrin to cause a selective activation of fibrin-bound plasminogen. All fibrinolytic drugs are administered IV. Streptokinase is antigenic, whereas reteplase is not. Thrombocytopenia is not normally caused by thrombolytic drugs.

SUPPLEMENTAL READING

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Case **Study**   Treatment of Thrombosis

A 23-year old pregnant woman who has been administered IV heparin for treatment of deep vein thrombosis has developed heparin-induced thrombocytopenia. Altering therapy by removing heparin and adding warfarin is not a viable option, because warfarin can cross the placenta and exert an anticoagulant effect in the fetus. Suggest a treatment approach.

ANSWER: Treatment of thrombosis can be initiated during pregnancy with infusion of argatroban, a direct inhibitor of thrombin. This drug does not cross the placenta and has not been reported to produce effects in the fetus. Argatroban is discontinued at the time of delivery, and thrombosis is then managed postpartum for 2 months with warfarin.