HEMATOPOIETIC SYSTEM MEDICATION

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I. Agents Used in Anemias

- Hematopoiesis, the production from undifferentiated stem cells of circulating erythrocytes, platelets, and leukocytes, is a remarkable process that produces over 200 billion new blood cells per day in the normal person and even greater numbers of cells in people with conditions that cause loss or destruction of blood cells
- requires **a constant supply of three essential nutrients** —iron, vitamin B 12, and folic acid— as well as the presence of hematopoietic growth factors
- Anemia=↓ with > 10% ofHb, Ht and nr. of H
- Agents used in anemias: iron, vitamin B12, FOLIC ACID

Agents Used in Anemias:

A. Iron

TABLE 33–1 Iron distribution in normal adults.[1]

	Iron Content (mg)	
	Men	*Women*
Hemoglobin	3050	1700
Myoglobin	430	300
Enzymes	10	8
Transport (transferrin)	8	6
Storage (ferritin and other forms)	750	300
Total	4248	2314

- 3.4-5 g
- Absorption: daily≈10-15 mg iron from diet→5-10% are absorbed (higher percentage if a deficit exists), mostly in duodenum and proximal jejunum→used for Hb synthesis, deposited as ferritin (liver, bones, spleen, Ma), deposited in intestinal ephitelial cells or remains in systemic circulation binded of transferrin (one molecule binds 2 molecules of iron)
- Involved in gastric acid secretion, cellular respiration, protective role for infection
- Deficit→iron deficit anemia =chronic, microcytic, hypochromic → pale skin, asthenia, tachycardia

Agents Used in Anemias:

A. Iron

- oral or parenteral
- Curative or prophylaxis (pregnancy, lactation, children in growth period, after gastric resection etc)

A. **Oral iron therapy**-correct the anemia very fast, if the intestinal absorption is not altered

-ferros iron is the most efficiently absorbed→ferrous salts

TABLE 33–3 Some commonly used oral iron preparations.

Preparation	Tablet Size	Elemental Iron per Tablet	Usual Adult Dosage for Treatment of Iron Deficiency (Tablets per Day)
Ferrous sulfate, hydrated	325 mg	65 mg	2–4
Ferrous sulfate, desiccated	200 mg	65 mg	2–4
Ferrous gluconate	325 mg	36 mg	3–4
Ferrous fumarate	325 mg	106 mg	2–3

Agents Used in Anemias: A. Iron

A. Oral iron theraphy

Drugs:

*Ferrous sulfate -Ferrogradumet troches 325mg(105mg Fe)
*Ferrous Gluconate-cpr 35mg
* Feros Glutamate -Glubifer troches 100mg
*Ferros Fumarate feros-oral suspension 3%
*Iron hydroxide polimaltose-Hausman iron sol 5%; syrup1%; Maltofer-with folic acid, chewing troches

Agents Used in Anemias: A. Iron

A. Oral iron theraphy

Common ***adverse effects*** of oral iron therapy include nausea, epigastric discomfort, abdominal cramps, constipation, and sometimes diarrhea-usually dose-related and can often be overcome by ↓ the daily dose of iron or by taking the tablets immediately after or with meals.

→Some patients have less severe gastrointestinal adverse effects with one iron salt than another

Agents Used in Anemias:

A. Iron

B. Parenteral iron therapy—should be reserved for patients with documented iron deficiency who are unable to tolerate or absorb oral iron and for patients with extensive chronic anemia who cannot be maintained with oral iron alone.

- This includes patients with advanced chronic renal disease requiring hemodialysis and treatment with erythropoietin, various post gastrectomy conditions and previous small bowel resection, inflammatory bowel disease involving the proximal small bowel, and malabsorption syndromes.

Agents Used in Anemias: A. Iron

B. Parenteral iron therapy

! Toxicity directly proportional with the dose : pain, local hyperpigmentation, fever, cephalalgia, alergic reactions , nausea, emesis

! Mandatory to be tested before administration

Agents Used in Anemias: A. Iron

B. Parenteral iron therapy

- The challenge with parenteral iron therapy is that parenteral administration of inorganic free ferric iron produces serious dose-dependent toxicity, which severely limits the dose that can be administered
- However, when the ferric iron is formulated as a colloid containing particles with a core of iron oxyhydroxide surrounded by a core of carbohydrate, bioactive iron is released slowly from the stable colloid particles.
- In the United States, the three available forms of parenteral iron are iron dextran, sodium ferric gluconate complex, and iron sucrose.

Agents Used in Anemias: A. Iron

B. Parenteral iron therapy

1. ***Iron-dextran complex***-50mg fier/ml solution; IM deep or IV-perfussion (iv: one dose and absence of local pain)

-↑ risk of allergic reactions

-adm. 1-2 ml daily or every 2 days

VENOFER 100MG

2. ***Iron sucrose complex***: 50mg/ml, vials 2ml; adm iv 2ml/day or every 2 days

3.Polimaltose iron complex 50mg Fe/ml, vials 5l; inj im, deep, 2ml every 2-3 days or IV

2 snd 3, lower risk of adverse reactions

FERINJECT 50MG/ml- vials2/5ML

Agents Used in Anemias: A. Iron

B. Parenteral iron therapy

! For patients treated chronically with parenteral iron, it is important to monitor iron storage levels to avoid the serious toxicity associated with iron overload

- Unlike oral iron therapy, which is subject to the regulatory mechanism provided by the intestinal uptake system, parenteral administration—which bypasses this regulatory system-can deliver more iron than needed→ serum concentrations of ferritin and the transferrin saturation, which is the ratio of the total serum iron concentration to the total iron-binding capacity (TIBC).

Agents Used in Anemias: A. Iron

Clinical Toxicity

A. **Acute Iron Toxicity**

-is seen almost exclusively in young children who accidentally ingest iron tablets- As few as 10 tablets of any of the commonly available oral iron preparations can be lethal in young children

- Children who are poisoned with oral iron experience necrotizing gastroenteritis, with vomiting, abdominal pain, and bloody diarrhea followed by shock, lethargy, and dysp- nea→severe metabolic acidosis, coma, and death. Urgent treatment is necessary
- Whole bowel irrigation should be performed to flush out unabsorbed pills
- **Deferoxamine**,a potent iron-chelating compound, can be given intravenously to bind iron

Agents Used in Anemias: A. Iron

Clinical Toxicity

A. Acute Iron Toxicity

-Activated charcoal, a highly effective adsorbent for most toxins, does not bind iron and thus is ineffective

- Appropriate supportive therapy for gastrointestinal bleeding, metabolic acidosis, and shock must also be provided

B. Chronic Iron Toxicity

- Chronic iron toxicity (iron overload), also known as hemochromatosis, results when excess iron is deposited in the heart, liver, pancreas, and other organs
- It can lead to organ failure and death
- Chronic iron overload in the absence of anemia is most effi- ciently treated by intermittent phlebotomy
- Iron chelation therapy using parenteral deferoxamine or the oral iron chelator deferasirox is less efficient

Agents Used in Anemias: VITAMIN B12

**Vitamin B 12 (cobalamin) serves as a cofactor for several essential biochemical reactions in humans.*

- *Deficiency →megaloblastic anemia, gastrointestinal symptoms, and neurologic abnormalities*

- *The average diet contains 5–30 mcg of vitamin B1 2 daily, 1–5 mcg of which is usually absorbed.*
- *is avidly stored, primarily in the liver, with an average adult storage pool of 3000–5000 mcg.*
- *Only trace amounts of vitamin B 12 are normally lost in urine and stool*
- *Because the normal daily requirements of vitamin B12 are only about 2 mcg, it would take about 5 years for all of the stored vitamin B12 to be exhausted and for megaloblastic anemia to develop if B12 absorption were stopped*
- *Vitamin B1 2 is absorbed after it complexes with intrinsic factor, a glycoprotein secreted by the parietal cells of the gastric mucosa*

Agents Used in Anemias: VITAMIN B12

- *Intrinsic factor combines with the vitamin B1 2*

that is liberated from dietary sources in the stomach and duodenum, and the intrinsic factor-vitamin B1 2 complex is absorbed in the distal ileum by a highly selective receptor-

mediated transport system

- *Vitamin B1 2 deficiency in humans most often results from malabsorption of vitamin B1 2 due either to lack of intrinsic factor or to loss or malfunction of the absorptive mechanism in the distal ileum*
- *Nutritional deficiency is rare but may be seen in strict vegetarians after many years without meat, eggs, or dairy products.*

Agents Used in Anemias: VITAMIN B12

Vitamin B12 is used to treat or prevent deficiency

-The most characteristic clinical manifestation of vitamin B1 2 deficiency is megaloblastic, macrocytic anemia, often with associated mild or moderate leukopenia or thrombocytopenia (or both), and a characteristic hypercellular bone marrow with an accumulation of megaloblastic erythroid and other precursor cells

-The neurologic syndrome associated with vitamin B1 2 deficiency usually begins with paresthesias in peripheral nerves and weakness and progresses to spasticity, ataxia, and other central nervous system dysfunctions

-Correction of vitamin B1 2 deficiency arrests the progression of neurologic disease, but it may not fully reverse neurologic symptoms that have been present for several months.

Agents Used in Anemias: Folic acid

-essential role in DNA synthesis

-contributes in vitamins A, E, K absorption

-daily necessary 50-200mcg→pregnancy 300-400mcg

-daily diet: 500-700mcg

-absorption-proximal jejunum

-storaged 5-20mcg, mostly in the liver

-urinary or in stool excretion

Clinic: anemia with symptoms similar to those of vit.B12 deficiency, excepting the neurological symptoms

Causes: insufficient incomme, chronic alcholism(insufficient income, altered deposits), treatment with phenitoin, etc)

Agents Used in Anemias: Folic acid

-troches1mg/5mg

-1-5mg/day until the correction of the cause -a la longue: malabsorption, insufficient income

-prophylaxis: pregnancy, chronic alcohol consumption, chronic liver diseases, haemolytic anemia, dialysis, dermatological diseases

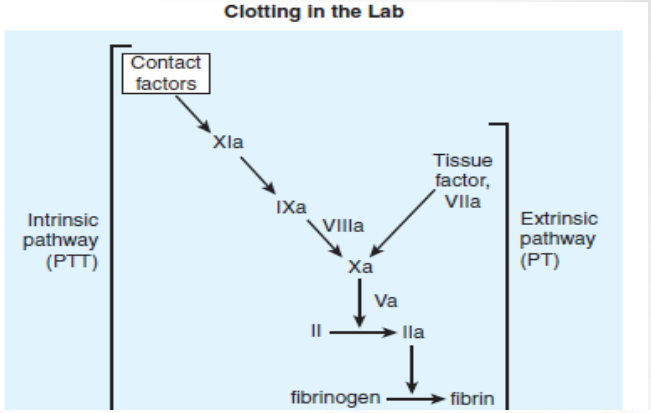
ANTICOAGULANTS

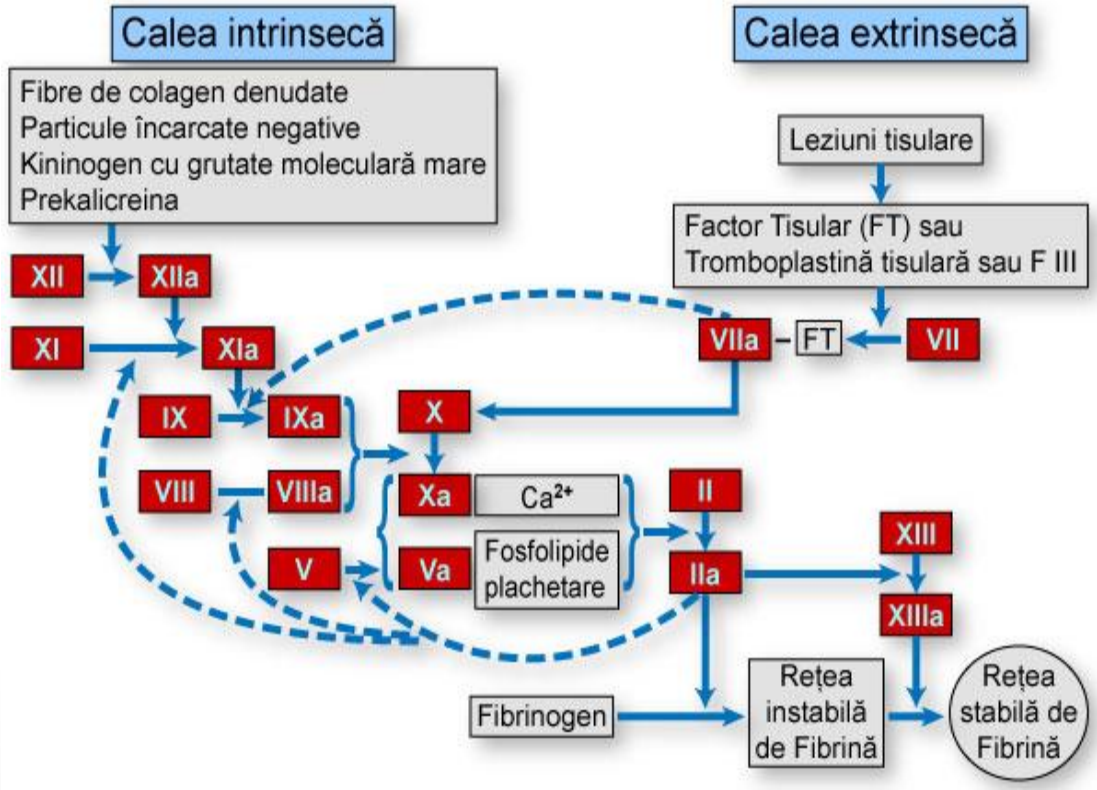
=drugs that stop the coagulation process preventing clot formation or the extension of the existing ones

-block the process of fibrinogen transforming in insoluble fibrin

→inhibit activity/formation

One/more coagulant factors





ANTICOAGULANTS

TABLE 34–1 Blood clotting factors and drugs that affect them.[1]

Component or Factor	Common Synonym	Target for the Action of:
I	Fibrinogen	
II	Prothrombin	Heparin (IIa); warfarin (synthesis)
III	Tissue thromboplastin	
IV	Calcium	
V	Proaccelerin	
VII	Proconvertin	Warfarin (synthesis)
VIII	Antihemophilic factor (AHF)	
IX	Christmas factor, plasma thromboplastin component (PTC)	Warfarin (synthesis)
X	Stuart-Prower factor	Heparin (Xa); warfarin (synthesis)
XI	Plasma thromboplastin antecedent (PTA)	
XII	Hageman factor	
XIII	Fibrin-stabilizing factor	
Proteins C and S		Warfarin (synthesis)
Plasminogen		Thrombolytic enzymes, amino-caproic acid

[1]See Figure 34–2 and text for additional details.

HEPARIN-indirect thrombin inhibitor

-a heterogeneous mixture of sulfated mucopolysaccharides; binds to endothelial cell surfaces and a variety of plasma proteins. Its biologic activity is dependent upon the endogenous anticoagulant

Antithrombin—> inhibits clotting factor proteases, especially thrombin (IIa), IXa, and Xa, by forming equimolar stable complexes with them- MPZ; in presence of heparine this effect is increased upon 1000x

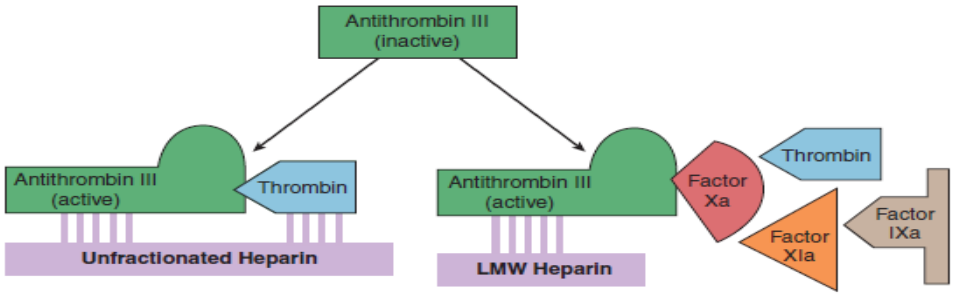


FIGURE 34–4 Cartoon illustrating differences between fondaparinux, low-molecular-weight heparins (LMWH), and high-molecular-weight heparin (HMWH, unfractionated heparin). Activated antithrombin III (AT III) degrades thrombin, factor X, and several other factors. Binding of these drugs to AT III can increase the catalytic action of AT III 1000-fold. The combination of AT III with unfractionated heparin increases degradation of both factor Xa and thrombin. Combination with fondaparinux or LMWH more selectively increases degradation of Xa.

ANTICOAGULANTS

HEPARIN

-Heparin functions as a cofactor for the antithrombin-protease reaction without being consumed

-Once the antithrombin-protease complex is formed, heparin is released intact for renewed binding to more antithrombin

-**High-molecular-weight (HMW),** also known as **UFH**, fractions of heparin with high affinity for antithrombin markedly inhibit blood coagulation by inhibiting all three factors, especially thrombin and factor Xa

-porcine or bovine origin

-Unfractionated heparin has a molecular weight range of 5000–30,000

-In contrast, the shorter- chain **low-molecular-weight (LMW)** fractions of heparin inhibit activated factor X but have less effect on thrombin than the HMW species. Nevertheless, numerous studies have demonstrated that

LMW heparins such as enoxaparin, dalteparin, and tinzaparin

are effective in several thromboembolic conditions

ANTICOAGULANTS HEPARIN

FK: inactive orally

!im→ risk of local hematoma→administed sc or inj iv

-hepatic metabolism, renal elimination

-dose in UI-1 UI =anticoagulant activity of 7.7mcg standard international

Indicatiions: profound venous thrombosis, myocardial infarction-acute, valve protesis, pulmonary embolism

UFH:

-pulmonary embolism 5000ui inj iv→ persion 1000ui/hour, 4-5 days or 4000ui every 4 hours

-prophylaxia (before surgical interventions): 5000ui, then 5000 every 8 hours, 1-2 weeks

ANTICOAGULANTS HEPARIN

Side effects

- bleeding: hematuria, haematoma, gi bleeding, nose bleed, gum bleeding, haemopthysis

!monitoring: partial tromboplastin time:1.5-2.5xN

-overdose: PROTAMINE SULPHATE (antidote) 1-1.5/1 (100-125mg for 000UI heparin)

- Trombocytopenia
- Allergic reactions

ANTICOAGULANTS HEPARIN

- Heparin is contraindicated in patients with hypersensitivity to the drug, active bleeding, hemophilia, significant thrombocy- topenia, purpura, severe hypertension, intracranial hemorrhage, infective endocarditis, active tuberculosis, ulcerative lesions of the gastrointestinal tract, threatened abortion, visceral carcinoma, or advanced hepatic or renal disease
- Heparin should be avoided in patients who have recently had surgery of the brain, spinal cord, or eye, and in patients who are undergoing lumbar puncture or regional anesthetic block.

ANTICOAGULANTS HEPARIN

LWH-fractioned- inhibit activated factor X but have less effect on thrombin than the HMW species. Nevertheless, numerous studies have demonstrated that

LMW heparins such as enoxaparin, dalteparin, and t inzaparin are effective in several thromboembolic conditions.

In comparison with UFH—have equal efficacy, increased bioavailability from the subcutaneous site of injection, and less frequent dosing requirements (once or twice daily is sufficient)

Indications same as UFH, adm. 1/day or 2/day

Drugs: nadroparin, enoxaparin, dalteparin, reviparin.

ANTICOAGULANTS HEPARIN

Low weight heparins:

*Enoxaparin (Clexane)-20mg/0.2ml; 40mg/0.2ml; 60mg/0.6ml; 80mg/0.8ml; 100mg/1m

*Nadroxaparin (Fraxiparine)-3800Ui anti Xa-0.4ml; 7600Ui anti Xa-0.8ml; 5700Ui anti Xa-0.6ml; 2850-0.3ml

*Dalteparin (Fragmin)-2500Ui/0.2ml; 5000UI/0.2ml; 2500Ui/ml-4ml; 10000ui/ml-1ml; 7500ui/0.3ml; 15000/0.6ml

*Reviparin (Clivarin) 1432UI/0.25ML

Side effects-fewer than not-fractioned ones

ORAL ANTICOAGULANTS

COUMARIN DERIVATES: acenocumarol, warfarin

=inhibit vit. K → inhibit forming ff II, VII, IX, X, inhibit proteins C and S

Indications:

-treatment and prophylaxis of profound venous thrombosis

- treatment and prophylaxis or pulmonary embolism

-prophylactic treatment of pulmonary embolisms that can appear in arythmias

-prophylaxis and treatment of embolic complications of myocardial infarction

ANTICOAGULANTS ORAL DRUGS

Side effects:

-bleeding

-skin necrosis (rare)

-gi perturbances

-allergia

-teratogenic effect!

CI: pregnancy, severe HTA, cerebral haemoragic event, history of bleeding ulcer

ANTICOAGULANTS ORAL DRUGS

*COUMARINE DERIVATES

- ***ACENOCUMAROL (SINTROM, TROMBOSTOP) TROCHES 2 AND 4 mg***

-in the evening, variable dose

-monitor Quick time and INR

- ***WARFARIN 2-10mg/day***

***!** Interactions: ↑ef: NSAIDs, antiplatelets, erytromicine*

↓ef: colestiramin (↓)absorption, carbamazepine, barbiturics, rifampicine

TABLE 34–2 Pharmacokinetic and pharmacodynamic drug and body interactions with oral anticoagulants.

Increased Prothrombin Time		Decreased Prothrombin Time	
Pharmacokinetic	*Pharmacodynamic*	*Pharmacokinetic*	*Pharmacodynamic*
Amiodarone	**Drugs**	Barbiturates	**Drugs**
Cimetidine	Aspirin (high doses)	Cholestyramine	Diuretics
Disulfiram	Cephalosporins, third-generation	Rifampin	Vitamin K
Metronidazole[1]	Heparin		**Body factors**
Fluconazole[1]	**Body factors**		Hereditary resistance
Phenylbutazone[1]	Hepatic disease		Hypothyroidism
Sulfinpyrazone[1]	Hyperthyroidism		
Trimethoprim-sulfamethoxazole			

[1]Stereoselectively inhibits the oxidative metabolism of the *S*-warfarin enantiomorph of racemic warfarin.

ANTICOAGULANTS ORAL DRUGS

New Oral Anticoagulant Drugs

→FDA approved **dabigatran etexilate**, a prodrug for dabigatran (**Pradaxa**®, Boehringer Ingelheim), rivaroxaban, a Factor Xa inhibitor (**Xarelto**®) and apixaban (**Eliquis**®, Bristol-Myers Squibb and Pfizer) for various specified indications

→**Dabigatran and apixaban** are approved to reduce the risk of stroke and thrombosis in patients with nonvalvular atrial fibrillation.

→**Rivaroxaban, the first Xa inhibitor**, is approved for multiple indications: reducing stroke risk in patients with nonvalvular atrial fibrillation, treatment of deep vein thrombosis (DVT) and pulmonary embolism and its recurrence, and DVT prophylaxis; 2.5/5mgx2/day

ANTIPLATELET DRUGS

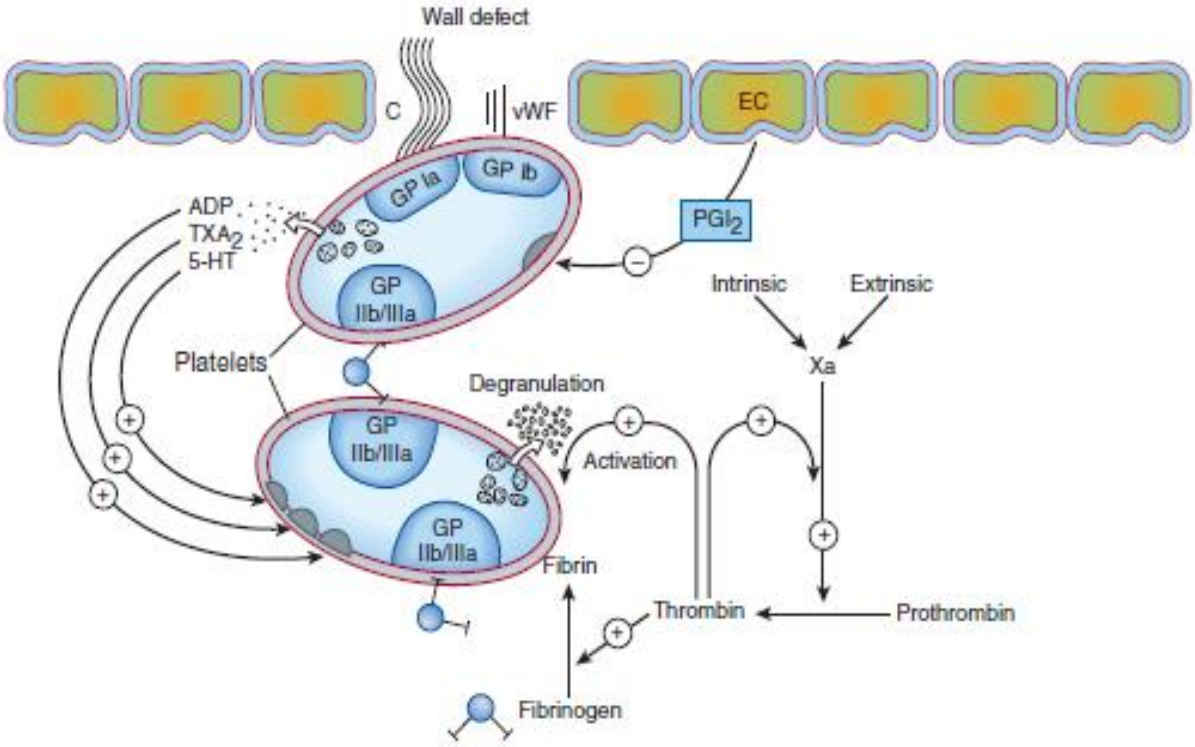


FIGURE 34–1 Thrombus formation at the site of the damaged vascular wall (EC, endothelial cell) and the role of platelets and clotting factors. Platelet membrane receptors include the glycoprotein (GP) Ia receptor, binding to collagen (C); GP Ib receptor, binding von Willebrand factor (vWF); and GP IIb/IIIa, which binds fibrinogen and other macromolecules. Antiplatelet prostacyclin (PGI_2) is released from the endothelium. Aggregating substances released from the degranulating platelet include adenosine diphosphate (ADP), thromboxane A_2 (TXA_2), and serotonin (5-HT). Production of factor Xa is detailed in Figure 34–2. (Redrawn and reproduced, with permission, from Simoons ML, Decker JW: New directions in anticoagulant and antiplatelet treatment. [Editorial.] Br Heart J 1995;74:337.)

ANTIPLATELETS

Classfication:

1.block COX→block production of TXA2 (effect depinds on blocking platelet COX)-sulfinpirazone, aspirin, other NSAIDs

2.Block the action of VIIIth factor of coagulation-dextran

3.↑AMPc, by stimulating adenilat-cyclase-prostacyclin=Iloprost, Enprostil or inhib.PDE-dipiridamol

4.block serotoninergic rr 5-HT2-ketanserina

5. Block platelets aggregation induced by adenosine phosphate→inh.fibrinogen binding to rr GP IIb/IIIa on platelets –ticlopidine and clopidogrel

6. Inhibit adenosine receptors: dipiridamol

ANTIPLATELETS

Indications:

-secondary prevention of haemoragic cerebral events

-preventing transitory cerebral ischemia

-primary and secondary prevention of miocadrial infarction

-unstable angina pectoris

-after aortic-coronary by-pass

ANTIPLATELETS

1. ***COX INHIBITORS***

***Aspirin: irreversible action** 75-100mg/day, block TXA2 production*

! High doses lose selectivity on platelet COX

***Sulfinpyrazone:** metabolite of phenylbutazone*

-reversible effect, short duration

-frequent side effects: gi disturbances, gastric erosions, anemia

ANTIPLATELETS

2. BLOCKERS OF VIIIa-DEXTRAN

=polysaccharide with animal origin, used as antithrombotic (antiplatelet), to reduce blood viscosity, and as a volume expander in hypovolaemia

-reversible inhibitor of platelets functions by blocking VIII factor →↑bleeding time

Side effects: skin rash, dizziness, anaphylactic reactions

3. ANTIPLATELETS THAT ↑AMPc

-Prostacyclin I2-Enprostenol or Iloprost (synthetic): inhibit aggregation, small vessels dilation, activate fibrinolysis

Indications: *pheripheric vasculopaties-Raynaud pneomenon*

ANTIPLATELETS

3. ANTIPLATELETS THAT ↑AMPc

-Dipiridamol:

-inh thrombocytes PDE →↑AMPc→↓adhesion

-inh. Myocite PDE →dilatation

-inhibit adenosine reuptake

-stimulate prostacyclin release from vascular endothelium

ANTIPLATELETS

5.. INHIBITORS OF ADENOSINE PHOSPHATE ADP INHIBITORS: TICLOPIDINA, CLOPIDOGREL

- ***TICLOPIDINA:*** *inh. Fibrinogen binding to GPIIb/IIIa rr, ADP dependent*
- *Side effects: hematologic disturbances, bleeding, skin rash, hepatic disturbances*

Indications: preventing cerebral events, dialysis, pheripheral arterial disease; 250mgx2/zi

- *CLOPIDOGREL: block irreversible and selective si ADP receptors on the platelets →stops fibrinogen bind to specific receptors*
- *Indications:preventing atherosclerotic complications, after surgical interventions-CV, pheripheral arterial disease:75mg/zi*

ANTIPLATELETS

7. Inhibitors of GPIIb/IIIa receptors

- *Abciximab: atc Ig G of rr GpIIb/IIIa (competitive antagonism); after coronary angioplasty*
- *Eptifibatid: an analog of the sequence at the extreme carboxyl terminal of the delta chain of fibrinogen, which mediates the binding of fibrinogen to the receptor*
- *Tirofiban is a smaller molecule with similar properties*
- *The three agents described above are administered parenterally*

HAEMOSTATICS

Hemostasis: vessel spasm (primary hemostasis), platelets aggregation and secondary hemostasis (insoluble fibrinogen →soluble fibrin)

Classification:

- ***Local hemostatics:*** *adrenaline, trombine, gelatin, metal salts (iron, aluminium)*
- ***Systemic hemostatics***

a. *Interfere with coagulation: vit.k, protamine, coagulation factors*
b. *Increase capillary resistance: carbazocrome, etamsilat, flavonoids*

- ***Block fibrinolysis:*** *aprotitine, aminocaproic acid*

LOCAL HEMOSTATICS

Mechanism:

-vasoconstriction: *adrenaline, noradrenaline-solution 1/100000-1/5000 in capillary bleeding, nose bleeding, superior digestive haemorragea, dental extractions*

-proteins precipitation: *iron chloride, aluminium chloride*

SYSTEMIC HEMOSTATICS

1. Interfere with coagulation factors

1.1 Vitamins k (fitomenadione) vials 10mg/ml, usually 20-80mg, in overdose of acenocumarol

1.2 Protamine sulphate-antidote in heparine overdose; vials 10mg/ml-5ml

1.3 Coagulation factors

SYSTEMIC HEMOSTATICS

2. ***Increase capillary resistance:***

→ ***CARBAZOCROME (ADRENOSTAZIN)-vials 1.5mg/5ml; inj iv 1-3/day***

→ ***ETAMSILAT-125mg/ml; 1-4/day***

! Not interfere with coagulation process

FIBRINOLYTIC DRUGS

-rapidly lyse thrombi by catalyzing the formation of the serine protease plasmin from its precursor, plasminogen

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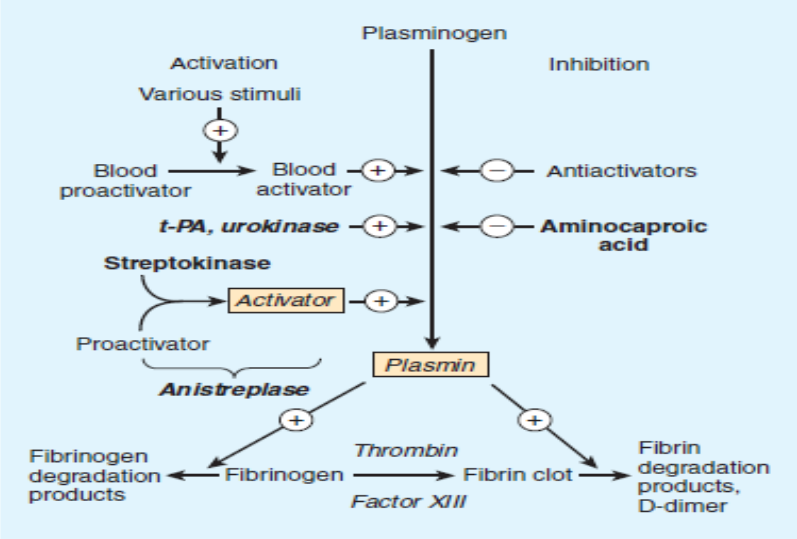

FIGURE 34–3 Schematic representation of the fibrinolytic system. Plasmin is the active fibrinolytic enzyme. Several clinically useful activators are shown on the left in bold. Anistreplase is a combination of streptokinase and the proactivator plasminogen. Aminocaproic acid (right) inhibits the activation of plasminogen to plasmin and is useful in some bleeding disorders. t-PA, tissue plasminogen activator.

FIBRINOLYTIC DRUGS

-natural or synthetic substances

**__Streptokinase__ is a protein synthesized by streptococci that combines with the proactivator plasminogen → This enzymatic complex catalyzes the conversion of inactive plasminogen to active plasmin*

***Urokinase** is a human enzyme synthesized by the kidney that directly converts plasminogen to active plasmin.*

FIBRINOLYTIC DRUGS

*-Plasminogen can also be activated endogenously by **tissue plasminogen activators (t-PAs).** These activators preferentially activate plasminogen that is bound to fibrin, which (in theory) confines fibrinolysis to the formed thrombus and avoids systemic activation*

Human t-PA is manufactured as a **ateplase by means of recombinant DNA technology.*

****Reteplase** is another recombinant human t-PA from which several amino acid sequences have been deleted. Reteplase is less expensive to produce than t-PA. Because it lacks the major fibrin-binding domain, reteplase is less fibrin-specific than t-PA*

****Tenecteplase** is a mutant form of t-PA that has a longer half-life, and it can be given as an intravenous bolus. Tenecteplase is slightly more fibrin-specific than t-PA.*

FIBRINOLYTIC DRUGS

-***Indications & Dosage***

Indications

-pulmonary embolism with hemodynamic instability

-severe deep venous thrombosis such as the superior vena caval syndrome, and ascending thrombophlebitis of the iliofemoral vein with severe lower extremity edema

-These drugs are also given intra-arterially, especially for peripheral vascular disease.

-management of acute myocardial infarction:

**Streptokinase is administered by intravenous infusion of a loading dose of 250,000 units, followed by 100,000 units/h for 24–72 hours*

FIBRINOLYTIC DRUGS

-***Indications & Dosage***

**Urokinase requires a loading dose of 300,000 units given over 10 minutes and a maintenance dose of 300,000 units/h for 12 hours*

**Alteplase (t-PA) is given by intravenous infusion of 60 mg over the first hour and then 40 mg at a rate of 20 mg/h*

**Reteplase is given as two intravenous bolus injections of 10 units each, sepa- rated by 30 minutes*

**Tenecteplase is given as a single intravenous bolus of 0.5 mg/kg*

**Anistreplase (where available) is given as a single intravenous injection of 30 units over 3–5 minutes*