In the name of Allah the Beneficent, the most merciful

We, the PharmaPill Team have tried our best to take all the doctor slides + his explanation .

We hope that this booklet will be most beneficial to you and we will post the notes on Anemia & antihyperlipidemic drugs soon later…

Wishing you all the best,

Pharma Pill team

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Preface:-

- Decreased clotting -- leads to – bleeding .

- Increased clotting – leads to – thrombus.

     ✓ Decreased clotting may be due to deficiency of clotting factors (where we need to either make blood transfusion or inject clotting factor to the patient) .

- Normal clotting time is 2-3 minutes.

- Normal prothrombin time is upto 15 min..

- In patients with reduced clotting factors, menorrhagia may occur.

- In cases of increased clotting, Thormbus may be formed which may lead to partial or complete blockage of blood circulation in an organ or a whole limb producing ischemia and infarction.

     ✓ If this occurs in brain or heart, deaeth consequently results.

• **Some are natural thrombolytic agents:**

- Heparin, plasmin, prostacyclin , NO and antithrombin III.

• **Some are natural thrombotic agents:**

- Thrombin, clotting factors , TXA2, Vit. K and fibrin

⊠ **Causes for thrombus formation :-**

- Most common world-wide known cause is atherosclerosis.

- Also Hypertension, Smoking and reduced free radicals detoxifications may prove important as etiology for it.

✓ Thrombus may form in arteries or veins.

- **Three factors play a major rule in thrombus formation:-**

    1- Platelets

    2- Fibrin formation

    3- clotting factors

To treat thrombus,

We inactivate these

✓   Major adverse effects of the drugs used in treatment is bleeding.

☑ DRUGS USED IN CLOTTING DISORDERS:

    1- DRGS THAT INCREASE CLOTTING.

    2- DRGS THAT INHIBIT CLOTTING.

- **DRUGS THAT INHIBIT CLOTTING -- ANTICLOTTING :**

    ⊠   Anticoagulants : (drugs which prevent clotting)

    ⊠   Thrombolytics : (drugs which inhibit clotting)

    ⊠   Fibrinolytics : (Drugs which causes lyses of fibrin)

    ⊠   Antiplatelets : (drugs which prevent and inhibit platelet aggression)

- **THROMBUS**: is the CLOT that adheres to vessel wall

- **EMBOLUS**: is the CLOT that floats in the blood

- **THROBOSIS**: is the formation of unwanted clot with in the blood vessel, producing : Acute myocardial infarction , Acute ischemic stroke , Deep vein thrombosis , Pulmonary embolism ,

    ✓   Arterial thrombosis is platelet rich clot is mostly caused by arthrosclerosis.

    ✓   Venous thrombosis is fibrin rich clot and is mostly caused by stasis of blood

- An injury to vascular system leads to interaction between Platelets, Endothelial system and Coagulation factors which results to formation of the CLOT

- Prostacycline and nitric oxide synthesized by intact endothelium prevents platelet aggregation.

3

1 **Resting platelets**

Resting platelets

Healthy, intact endothelial cells

Sub-endothelium

Collagen fibers

Inactive GP IIb/IIIa receptors

Ca^{2+} Ca^{2+} sequestered Ca^{2+} Ca^{2}

Ca^{2+}

$\ominus$

ATP → **cAMP**

5'-AMP

Prostacyclin
Nitrous oxide

Endothelial cells

2
- Healthy, intact endothelium releases prostacyclin into plasma.
- Prostacyclin binds to platelet membrane receptors, causing synthesis of cAMP.
- cAMP stabilizes inactive GP IIb/IIa receptors and inhibits release of granules containing platelet aggregation agents or Ca^{2+}.

3 **Platelet adhesion**

Resting platelets

Activated platelets cover and adhere to exposed subendothelial surface of damaged endothelium.

Collagen fibers

4 **Platelet activation**

Thromboxane A_2
ADP
Serotonin
PAF

Chemical mediators released by platelets

Activated platelets release chemical mediators

5 **Platelet aggregation**

Thromboxane A_2
ADP
Serotonin
PAF

Platelets are recruited into the platelet plug

$\oplus$

Figure 20.2
Formation of a hemostatic plug. (Continued on facing page.)

9 **Fibrinolysis**

Tissue plasminogen activator

Plasminogen → Plasmin → Fibrin peptides

8 **Formation of platelet-fibrin plug**

Prothrombin

Thrombin

Activation of coagulation factors in plasma

Fibrinogen → Fibrin

Heparin

Platelet-fibrin clot

Thrombin
ADP
Other mediators

Thromboxane A$_2$

7 Elevated Ca^{2+} causes:
- Release of platelet granules
- Activation of thromboxane A$_2$ synthesis
- Activation of the GP IIb/IIIa receptors

Granules

Ca^{2+}

Thromboxane A$_2$

Ca^{++} Ca^{++}

Prostaglandin H

Ca^{++}

Arachidonic acid

Ca^{2+}

Active GP IIb/IIIa receptors

Fibrinogen

6 Thrombin, thromboxane A$_2$, ADP, and other mediators released from activated platelets bound to collagen of the sub-endothelia cause an increase in Ca^{2+} levels.

Thromboxane A$_2$

Thrombin   ADP

Figure 20.2 (continued)
Formation of a hemostatic plug. PAF = platelet-activation factor.

Resting platelet

Activated platelet
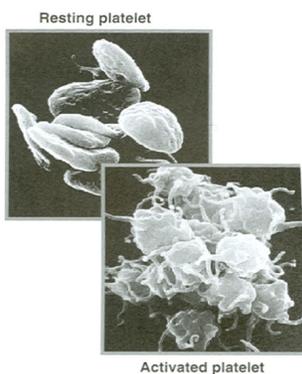
Figure 20.3
Scanning electron micro-graph of platelets.

Platelet activation

Platelet aggregation

Fibrinogen

Active GP IIb/IIIa receptors
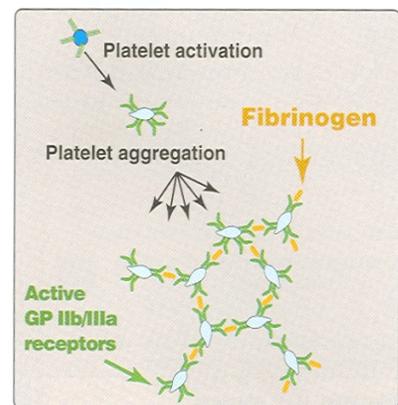
Figure 20.4
Activation and aggregation of platelets. GP = glycoprotein.

A) DRUGS WHICH INHIBIT PLATELET ACTIVITY.

- Aspirin ,ticlopidine , clopidogrel , abciximab , eptifibatide , tirofiban , dipyridamole.

B) DRUGS WHICH INHIBIT COAGULATION

- Thrombin inhibitors: Heparin and low-molecular-weight heparins

- ✓ **Other thrombin inhibitors :** Lepirudin , Danaparoid

- ✓ Vitamin K antagonists : Warfarin , Dicumarol

- ✓ **THROMBOLYTIC DURGS:** (Fibrinolytic drugs) Streptokinase , Alteplase ,Reteplase

Drugs affecting platelet function:

	Mechanism of action	Drug	ROA
(1)	Inhibition of prostaglandin metabolism	Aspirin	Oral
(2)	Inhibition of ADP-induced platelet aggregation (Antagonist of ADP receptors)	Clopidogrel Ticlopidine	Oral
(3)	GP IIb / IIIa receptor antagonists (Inhibitors)	Abciximab Tirofiban Eptifibatide	I / V
(4)	Phosphodiestrase 3 (PDE) inhibitors / adenosine uptake inhibitors	Dipyridamol Cilostazol	Oral

Aspirin:

Mechanism of action:

- irreversible inhibition (acetylation) of cyclooxygenase enzyme (that's why it is preferred over all other NSAID)..

  ✓ thus inhibits the synthesis of thromboxane A2 (thromboxane A2 ---- causes platelet aggregation)
    - Throboxane A2 activates platelet, makes it to change shape, release granules and aggregate.

– **Note that** : Other NSAIDs cannot acetylate cycloxygenases , therefore they have short duration of action and are reversible.

  ✓ A caution should be followed once Aspirin is used ebcause if the dose is raised it will non-selectively inhibit all PGs including Prostacycline.
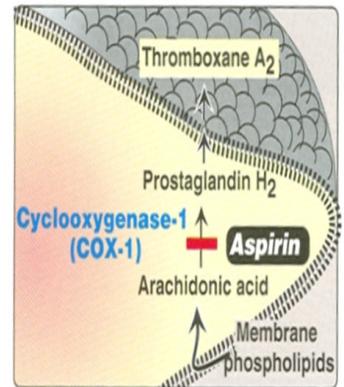
Figure 20.5
Aspirin irreversibly inhibits platelet cyclooxygenase-1.

Uses:
✓ Prophylaxis of thromboembolism e.g. unstable angina / myocardial infarction , ischemic stroke

Adverse effects:
✓ Hyperacidity

Contraindication:
✓ Peptic ulcer

Clopidogrel & Ticlopidine

Mechanism of action:

- Reduce platelet aggregation by Irreversibly block of ADP receptors on platelets.
  ✓ They have no effect on prostaglandins
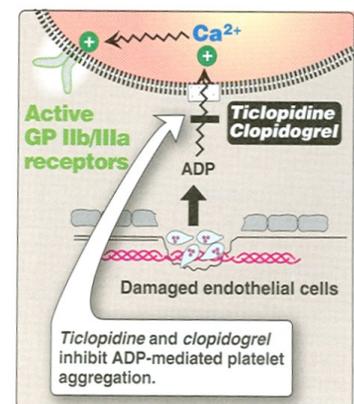
Figure 20.7
Mechanism of action of *ticlopidine* and *clopidogrel*. GP = glycoprotein.

Uses:

- To prevent thrombosis
- (Prevention of vascular events in pts with):
  - ✓ transient ischemic attacks
  - ✓ completed strokes
  - ✓ unstable angina pectoris
  - ✓ placement of a coronary stent.

Pharmacokinetic :

- Absorption of Ticlopidine is interferd by food
- On oral absorption both drugs bind to plasma proteins extensively
- These are metabolized in liver by CYP450 to active metabolites
- maximum effect is achieved in 3-5 days
- These are excreted in urine and feces both.
- It is given in a dose of 250mg twice daily in <u>clopidogrel</u> but only once for <u>Ticlopidine</u>.

Ticlopidine

Adverse effects: includes

- nausea , dyspepsia , diarrhea   20%
- hemorrhage 5%
- leucopenia(neutropenia) (most serious) 01%
- TTP (thrombotic thrombocytopenic purpura)
- it inhibits CYP450 affects metabolim of other drugs (when other drugs are co-administered with ticlopidine, their plasma level will be raised and metabolism will be reduced (Adverse effects))

Precaution: Regular monitoring of WBC count during first three months

Clopidogrel

Adverse effects:

- same but <u>fewer than ticlopidine</u>
- long duration of action (once daily dosing, ticlopidine given twice daily)
- 300 mg will inhibit 80% of platelet activity
- maximum effect is achieved in 3-5 days
- due to these properties it is preferred over Ticlopidine Also, it does NOT cause leucopenia.

Abciximab , Tirofiban , Eptifibatide:

- Abciximab is a monoclonal antibody directed against GPIIb /IIIa.

Mechanism of action:

- These drugs are GP IIb / IIIa receptor Blockers (antagonists)
  - ✓ GP IIb / IIIa complex on platelet surface is a receptor complex for :
    - fibrinogen
    - vitronectin
    - fibronectin
    - von Willebrand factor

   - ✓ Activation of this receptor complex is the "final common pathway" for platelet aggregation
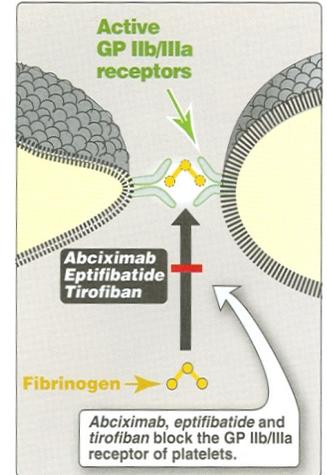
Figure 20.8
Mechanism of action of glycoprotein (GP) IIb/IIIa–receptor blockers.

Abciximab , Tirofiban , Eptifibatide

✓ These drugs are administered parentally and preferably by intravenous infusion
✓ These are excreted via kidneys where as abciximab is excreted unchanged.

Uses:

- To prevent thrombosis (Prevention of vascular events in pts with):
  - ✓ Acute coronary syndrome
  - ✓ Percutaneous coronary intervention

⊠ They can cause bleeding.

⊠ Only used in serious conditions or during coronary surgery or catheter introduction preventing platelets aggregation and subsequent vascular obstruction.

Dipyridamol:

- vasodilator(coronary) in large doses

- inhibits platelet function by inhibiting adenosine uptake & cyclic GMP phosphodiestrase activity

- increases intracellular level of cAPM resulting in decrease of thromboxane A2.

Uses:

- - Itself has little or no beneficial effect when used alone , therefore given in combination with :

    ✓ aspirin --- to prevent cerebrovascular ischemia.

    ✓ warfarin --- for prophylaxis of thromboemboli in pts with prosthetic heart valves.

Cilostazole:

- phosphodiestrase inhibitor(on PDE3)

- promotes vasodilation & inhibition of platelet aggregation

Uses:

- intermittent claudication

Antiplatelet drugs

- **Monitoring:**

    - Bleeding time (Antiplatelet drugs increase bleeding time).

Anticoagulants

- Inhibit development and enlargement of Clot
- Do not affect ---- fibrinolytic mechanism
- Not lyse the Clot

Heparin:

UFH [Unfractionated (Standard) heparin]
[HMWH (High molecular weight heparin)]
LMWH (Low molecular weight heparin)

    Enoxaparin
    Dalteparin
    Tinzaparin
    Ardeparin
    Danaparoid

Route of administration (in contrast to warfarin)

- I / V
- S.C.
- I / M (never) :Due to   danger of hematoma formation

Enoxaparin ----- S.C.   Tinzaparin ----- S.C.

Dalteparin ----- S.C.   Fondaparinux ---- S.C.

Pharmacokinetics

- Follows zero order kinetics

Heparin and LMWH are mostly confined to the vascular system

Heparin: IV, deep SC
LMWHs: SC

Partially degraded *heparin* and *LMWHs* appear in the urine.
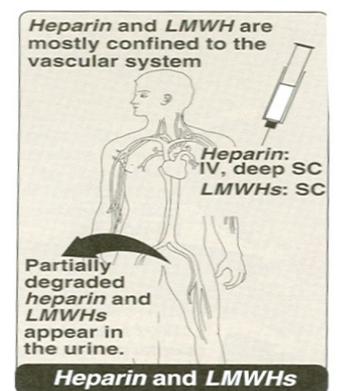
Heparin and LMWHs

Figure 20.16
Administration and fate of *heparin* and *low-molecular-weight heparins* (LMWHs).

Mechanism of action

- **Acts by inhibiting activated clotting factors in the blood**
- ⊠ Bind Antithrombin (a plasma protease inhibitor) => ↻ activity (1000-fold) of Antithrombin, which inactivates (inhibits) serine proteases (Activated Clotting factors) <u>IIa</u> (Thrombin), IXa, <u>Xa</u>, XIa, & XIIa by forming complex with them

- **UFH, LMWH & fondaparinux:**
    - ✓ ↻ inactivation of factor <u>Xa</u>

- **UFH & to a lesser extent LMWH:**
    - ✓ also ↻ inactivation of thrombin (factor <u>IIa</u>)

Heparin :Action

- Both :in vivo & in vitro (in contrast to warfarin which is orally given and only active in vivo)
- Onset of action :immediate (because it acts on → preformed blood components in contrast to warfarin)
- **Site of action**:   Blood
- Termination of action
- Duration of therapy

Figure 20.10
Formation of fibrin clot .

Uses

1. **In Vivo** :to prevent thromboembolism
    - prevention of pulmonary emboli in pts with established Deep vein thrombosis (DVT)
    - pulmonary embolism
    - acute coronary syndrome (unstable angina / myocardial infarction)
    - prosthetic heart valves
    - -Bed ridden patients
    - Postoperatively (e.g. hip replacement)
    - With thrombolytics →for revascularization
    - With glycoprotein IIb/IIIa receptors inhibitors → during angioplasty placement of coronary stent

2. **In Vitro:**
    - During hemodialysis
    - does not cross placenta   ----DOC in   pregnancy

Adverse effects:

  - Bleeding
  - Hypersensitivity reactions
  - Alopecia
  - In long-term therapy :
    - ✓ Osteoporosis & spontaneus fracture
    - ✓ Mineralocorticoid deficiency (Hypoaldosteronism)

Adverse effects: days.

Thrombosis : As use of heparin may lead to reduction in the activity of antithrombinIII.

Thrombocytopenia : Is an abnormality with few numbers of platelets in circulation
  - **Transient (HIT)/type I**
    - ✓ within first 5 days and is not serious

  - **Severe /Type II**
    - ✓ antibody-mediated   cause platelet aggregation and release of platelet contents.This can lead to thrmobocytopenia and THROMBOSIS occur 5-14 days after first exposure

 treatment :
  - d/c heparin
  - direct thrombin inhibitor such as lepirudin

Heparin: Monitoring
  - aPTT --- (activated partial thromboplastin time) for UFH (not for LMWH & fondaparinux)
  - platelet count

Heparin :Precaution
  - allergic patients
  - pregnancy (not contraindication) because it does not cross placenta.

Contraindications:

- ⊠ Hypersensitivity to drug
- ⊠ active bleeding
- ⊠ intracranial hemorrhage
- ⊠ hemophilia
- ⊠ significant thrombocytopenia
- ⊠ purpura
- ⊠ severe / malignant hypertension
- ⊠ dissecting aortic aneurysm
- ⊠ recent stroke
- ⊠ infective endocarditis
- ⊠ active tuberculosis
- ⊠ ulcerative lesions of the GIT (duodenal ulcer)
- ⊠ threatened abortion
- ⊠ visceral carcinoma
- ⊠ advanced hepatic or renal disease
- ⊠ recent surgery of brain, spinal cord, or eye or patients undergoing lumbar puncture or regional anesthetic block
- ⊠ LMWH use --- is discouraged or contraindicated in Patients with renal insufficiency , Bleeding disorders , Alcoholics , Having had surgery of brain ,eye , spinal cord

LMWH , incomparison with UFH,

efficacy	Equal
bioavailability	greater
t ½ & durations of action	longer
dose frequency	less (once or twice a day)
Adverse effects	Less likely to cause thrombosis & thrombocytopenia
Antidote	Protamine --(partially effective)
Anticoagulant response	Predictable

- More consistent relationship between dose & therapeutic effect, allowing anticoagulant control without laboratory test (No monitoring with aPTT)

Fondaparinux:

- Long half life →15 hours
- Once daily dosing

Uses

- in preventing development of asymptomatic DVT
- in combination with warfarin --- in treatment of acute venous thromboembolic disease

⊠ **Increased bleeding in patients:**
  - ✓ administered drug sooner than 6 hours postoperatively
  - ✓ weigh less than 50 Kg
  - ✓ renal insufficiency

Heparin Reversal:

- d/c drug
- protamine sulphate ---- highly basic
- Neutralization of LMWH by protamine is   --- incomplete
- Protamine not reverse the effect of fondaparinux

o **Direct thrombin inhibitors**

- bind thrombin without additional binding proteins, such as antithrombin

Lepirudin:

- short half life 1.3 hours

- Use to replace heparin-in a condition where heparin has produced thrombocytopenia

- Duration of action increased in renal insufficiency
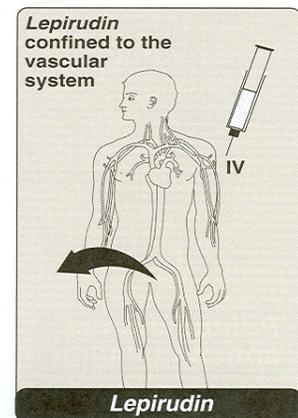
Figure 20.18
Administration of *lepirudin*.

Coumarin anticoagulants: Warfarin:

- Route of administration: oral

- Bioavailability: 100%

- Plasma albumin binding: 99%

- Volume of distribution: small

- Plasma half life: 36 hours

- Elimination depends on: metabolism by cytochrome P450 enzymes

- Lack of urinary excretion of unchanged drug

Mechanism of action

- Inhibit synthesis of clotting factors in liver by inhibiting vitamin K reductase

✓ Blockade results, in incomplete molecules that are biologically inactive in coagulation

Onset of action: delayed

- There is 8- to 12-hour delay in the action but complete effect is achieved in 72 hours

- Anticoagulant effect results from a balance between partially inhibited synthesis & unaltered degradation of the four vitamin K-dependent clotting factors in circulation

Factors	VII	IX	X	II
t ½ (Hours)	6	24	40	60

- Produce hypoprothrombinemia

Uses:

- same as Heparin, except in pregnancy: e.g.
  - ✓ Rheumatic heart disease
  - ✓ valve replacement
  - ✓ atrial fibrillation
  - ✓ unstable angina / myocardial infarction
  - ✓ heart failure

adverse effects

- Crosses placenta readily & can cause a hemorrhagic disorder in fetus
- Can cause serious birth defects characterized by abnormal bone formation
- Should never be administered during pregnancy
- Transient hypercoagulability due to decrease protein C
- Reduced activity of protein C => Cutaneous necrosis (soft tissue necrosis) frank infarction of breast, fatty tissues, intestine, & extremities
- Pathologic lesion associated with hemorrhagic infarction is venous thrombosis, suggesting that it is caused by warfarin-induced depression of protein C synthesis
- Bleeding
- Alopecia
- Purple toe syndrome
-

Warfarin Monitoring

- prothrombin time
- INR (international normalized ratio)

Drug interactions

· **Increase prothrombin time**

  - o **Pharmacokinetic interactions**
    - ▪ Amiodarone
    - ▪ Cimetidine
    - ▪ Metronidazole
    - ▪ Fluconazole
    - ▪ Trimethoprim-sulfamethoxazole

· **<u>Increase prothrombin time</u>**

    o **Pharmacodynamic interactions**

        ▪ <u>Drugs:</u>
- ✓ Aspirin (high doses)
- ✓ Cephalosporins, 3rd generation
- ✓ Heparin

        ▪ <u>Diseases:</u>
- ✓ Hepatic disease
- ✓ Hyperthyroidism

· **<u>decrease prothrombin time</u>**

    o **Pharmacokinetic interactions**

        ▪ Barbiturates

        ▪ Rifampin

    o **Pharmacodynamic interactions**

        ▪ <u>Drugs:</u>
- ✓ Diuretics
- ✓ Vitamin K

        ▪ <u>Body factors:</u>
- ✓ Hereditary resistance
- ✓ Hypothyroidism

Reversal of action

- Stop the drug
- Vitamin K1 (Phytonadione)   oral ; i / v
- FFP (Fresh-frozen plasma)
- Prothrombin complex concentrates (PCC)   such as
- Bebulin & Proplex T
- rFVIIa (recombinant factor VIIa)

Contraindications

⌦ Pregnancy

⌦ Active or past G.I. ulceration

⌦ Significant thrombocytopenia

⌦ Severe / malignant hypertension

⌦ Bacterial endocarditis

⌦ Hepatic or renal disease

⌦ Recent surgery of brain, spinal cord, or eye

⌦ Chronic alcoholism

Major differences between Heparin and warfarin

Drugs and their properties	Heparin	Warfarin
Route O A	IV or SC	Orally
Action	In vitro and in vivo	Only in vivo
M O Action Monitering	Inhibit Xa and IIa By aPTT.	Inhibits Vit. K reductase By Prothrombin time and INR
Onset of action	immediate	Takes 36 hours to reach its maximal eficacy
Overdose treatment	Protamine and lepurdine	Vit. K1, FFP, rClotting factors, PCC
Clinical usage	Used in pregnancy	NEVER used in pregnancy
Major adverse effects	Hypersensitivity thrombosis &thrombocytopenia.	Hypercoagulability and reduced protein C ➲ necrosis.

FIBRINOLYTICS (Thrombolytics)

- ✓ Streptokinase
- ✓ Urokinase
- ✓ Anistreplase

t-PA (Tissue plasminogen activator) :

- ✓ Alteplase
- ✓ Reteplase
- ✓ Tenecteplase

Administered ----- intravenously

Fibrinolytics (Thrombolytics)

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

Streptokinase:

- is a protein (but not enzyme in itself) synthesized by β-hemolytic streptococci combine with proactivator zymogen plasminogen

  - ✓ this enzymatic complex catalyzes the conversion of other inactive plasminogen to active plasmin

Disadvantages:

- ☒ Antigenic

- ☒ Nonspecific, can result in systemic fibrinolysis

Urokinase:

- is a human enzyme synthesized by the kidney

- directly converts plasminogen to active plasmin

Disadvantages:

- ☒ lack fibrin specificity, cause systemic fibrinolysis
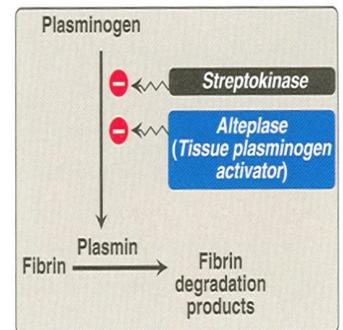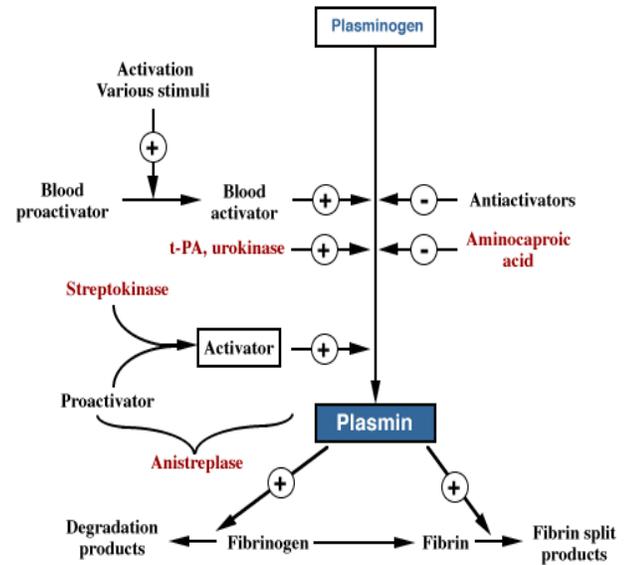
Figure 20.21
Activation of plasminogen by fibrinolytic agents.
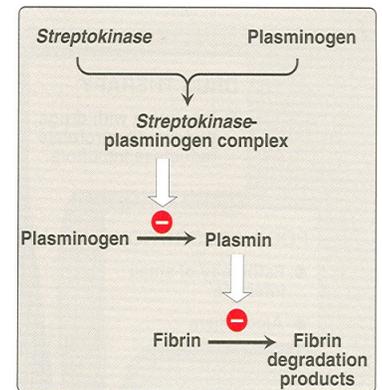
Figure 20.25
Mechanism of action of *streptokinase.*

Anistreplase: (APSAC: anisoylated plasminogen streptokinase activator complex)

- consists of a complex of purified human plasminogen & bacterial streptokinase that has been acylated to protect the enzyme's active site

  ✓ When administered, the acyl group spontaneously hydrolyzes, freeing the activated streptokinase-proactivator complex

- this product allows for:

  ✓ rapid intravenous (bolus) injection where as (SK given by infusion)

  ✓ longer duration of action

  ✓ more thrombolytic activity

  ✓ greater clot selectivity (i.e., more activity on plasminogen associated with clot than on free plasminogen

t-PA (Tissue plasminogen activator) :

  ✓ Alteplase

  ✓ Reteplase

  ✓ Tenecteplase

- Activate plasminogen endogenously

- t-PA is a large human protein that preferentially activate plasminogen i.e. bound to fibrin, which (in theory) confines fibrinolysis to the formed thrombus & avoids systemic activation

- Nonantigenic

- Fibrin specific
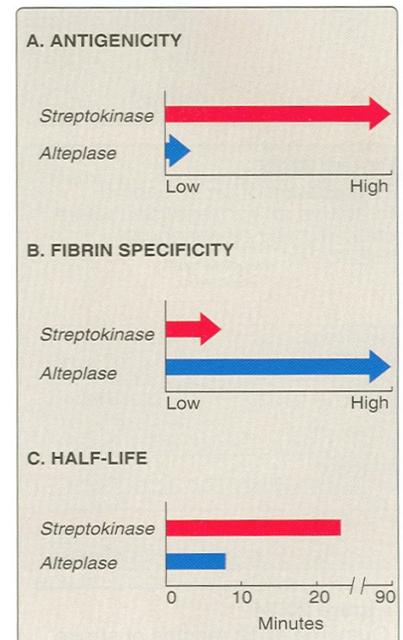
Figure 20.22
A comparison of *streptokinase* and *alteplase*.

Reteplase, as compared to t-PA:
  - less expensive
  - less fibrin specific

Tenecteplase, as compared to t-PA:
  - faster onset of action
  - longer DOA (longer $t_{1/2}$)
  - more fibrin specific

Uses of Fibrinolytics (Thrombolytics)

- Acute thromboembolic diseases:
  - · Pulmonary embolism
  - · Central deep venous thrombosis such as:
    - ✓ Superior vena caval syndrome
    - ✓ Ascending thrombophlebitis of iliofemoral vein
  - · Peripheral vascular disease --- (ROA --- intra-arterial)
  - · Acute myocardial infarction (PCI: percutaneous coronary intervention)
  - · Acute ischemic stroke (cerebral hemorrhage must be positively ruled out)

Adverse effects of Streptokinase

⊠ Antigenic (immunogenic)
⊠ Hypersensitivity reactions
⊠ pts with antistreptococcal Abs. can develop --- fever, allergic reactions & therapeutic resistance

Adverse effects of Fibrinolytics (Thrombolytics)

⊠ Bleeding ----- cerebral hemorrhage (hemorrhagic stroke)

Treatment of bleeding due to thrombolytics

- Whole blood , Packed red cells , FFP , Aminocaproic acid

  ✓ During usage of any type of clotting treatments, clotting time should be carefully monitored that it does not exceed beyond double the normal value

Contraindications of Fibrinolytics (Thrombolytics)

- **Similar to anticoagulants:**

⊠ Surgery within 10 days, including : organ biopsy , puncture of noncompressible
   vessels , serious trauma , cardiopulmonary resuscitation

⊠ Serious gastrointestinal bleeding within 3 months

⊠ History of hypertension (diastolic BP > 110 mmHg)
      ✓ severe / uncontrolled / malignant hypertension

⊠ Active bleeding

⊠ Peptic ulcer

⊠ Hemorrhagic disorder

⊠ Previous cerebrovascular accident

⊠ Active intracranial process

⊠ Aortic dissection

⊠ Acute pericarditis

Drugs used in bleeding disorders (to facilitate clotting)

1. Vitamin K

2. Replacement factors (Plasma fractions)

3. Fibrinolytic inhibitors (Antiplasmin drugs):

      a. EACA (Epsilon aminocaproic acid)

      b. Tranexamic acid ---- an analog of aminocaproic acid

      c. Aprotinin

Vitamin K:

- Natural forms of Vitamin K:
      a. Vitamin K1 (Phytonadione)
      b. Vitamin K2 (Menaquinone)

- fat-soluble
      ✓ Require bile salts for absorption from GIT
- It can be administered ---- oral , I / V
- Participate postribosomal modification of prothrombin & factors VII, IX, X

Uses

- Vitamin K deficiency
   - ✓ In Newborns to prevent the hemorrhagic disease of vitamin k deficiency , esp. in premature infants
- Pts in ICUs   --- due to
   - ✓ poor diet , parenteral nutrition , recent surgery , multiple antibiotic therapy , uremia

Adverse effects

⊠ I / V administration should be slow, because rapid infusion can produce dyspnea, chest & back pain, & even death

Fibrinolytic inhibitors (Antiplasmin drugs)

| Drug	ROA
EACA (Epsilon aminocaproic acid)	orally; intravenously
Tranexamic acid ---- an analog of aminocaproic acid	
Aprotinin	intravenously

EACA (Epsilon aminocaproic acid)

Pharmacokinetics:

rapidly absorbed orally

cleared by kidney

Fibrinolytic inhibitors ----- EACA (Epsilon aminocaproic acid)

& Tranexamic acid ---- an analog of aminocaproic acid

Mechanism of action:

- is a synthetic inhibitor of fibrinolysis
- competitively inhibits plasminogen activation
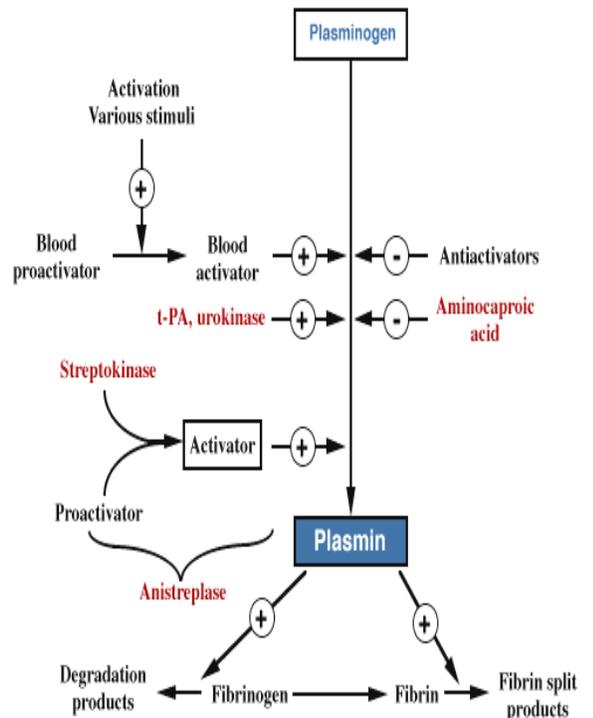
Uses

- adjunctive therapy in hemophilia
- bleeding from fibrinolytic therapy
- prophylaxis for rebleeding from intracraneal aneurysm
- postsurgical gastrointestinal bleeding,
- postprostatectomy bleeding,
- bladder hemorrhage sec. to radiation- & drug-induced cystitis

Adverse effects:

⊠ intravascular thrombosis

⊠ hypotension

⊠ myopathy

⊠ abdominal discomfort

⊠ diarrhea

⊠ nasal stuffiness

Contraindications:

⊠ DIC (Disseminated intravascular coagulation)

⊠ Genitourinary bleeding of upper tract, e.g., kidney & ureters, because of the potential for excessive clotting.

Aprotinin (Serine protease inhibitor)

Mechanism of action:

- Inhibits fibrinolysis by free plasmin
- Also inhibits plasmin-streptokinase complex

Uses

- Surgery involving extracorporeal circulation for open heart procedures & liver transplantation
- Coronary artery bypass grafting

Adverse effects:

⊠ Anaphylaxis

Precaution: small test dose