

Lecture. DRUGS ACTING ON BLOOD COAGULATION AND FIBRINOLYSIS (dental faculty)

HAEMOSTASIS AND FIBRINOLYSIS

Hemostasis is the arrest of bleeding from damaged blood vessels. It is complex cascade of enzymatic reactions.

Damage of blood vessel " vasospasm " platelet aggregation and adhesion " formation of platelet plug " activation of clotting factors " conversion of fibrinogen to insoluble fibrin " clot formation " stop of bleeding.

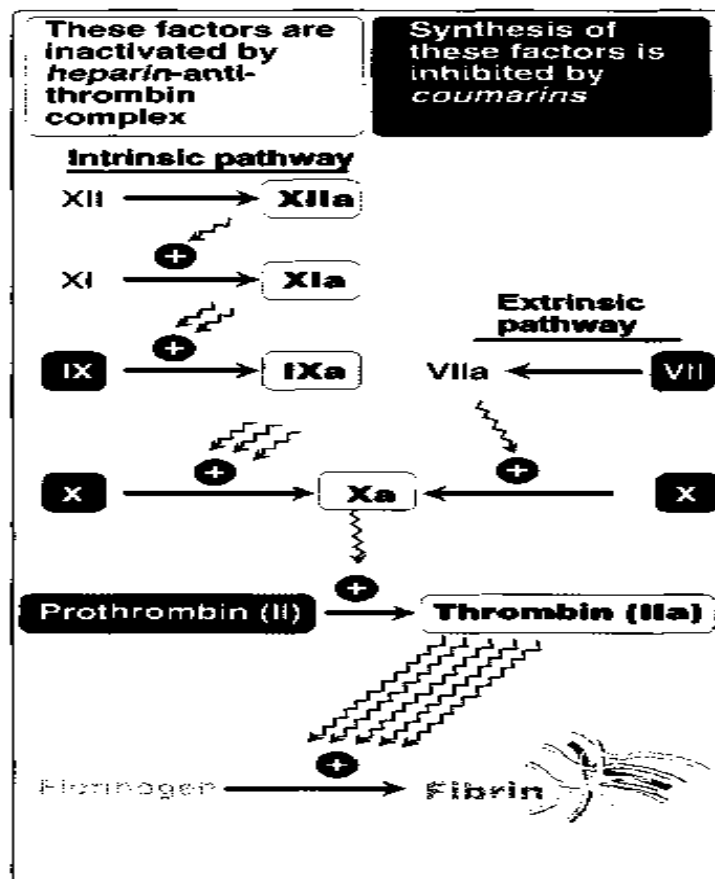
Natural clotting limitation factors are heparin and antitrombin III

Fibrinolysis is lysis of thrombus for restoration of blood flow: plasminogen (pro-fibrinilysin) " plasmin (fibrinolysin) " lysis of fibrin clot.

Pathology of haemostasis and fibrinolysis:

- decrease in blood coagulation and (or) increase in fibrinolysis " bleeding
- increase in blood coagulation and (or) decrease in fibrinolysis " thrombosis, thromboembolism, syndrome of disseminated intravascular blood coagulation.

FORMATION OF FIBRIN CLOT



DRUGS AFFECTING BLOOD COAGULATION AND FIBRINOLYSIS

1. Coagulants (they increase blood coagulation)
2. Anticoagulants ((they decrease blood coagulation)
3. Anti-platelet drugs ((they decrease platelet aggregation)
4. Fibrinolytic drugs ((they increase fibrinolysis)
5. Inhibitors of fibrinolysis ((they decrease fibrinolysis)

COAGULANTS

Classification

1. Direct-acting (are active in vivo as well as in vitro)

Thrombin
Fibrinogen
Calcium chloride
Calcium gluconate
Gelatina medicinalis

2. Indirect-acting (are active only in vivo)

Vitamin K (Phytomenadion)
Vikasolum

DIRECT-ACTING COAGULANTS

Thrombin is active compound of blood coagulation system, is used for bleeding from small vessels, only topically (IV administration may cause disseminated thrombosis).

Fibrinogen is non-active compound of blood coagulation system, is used for bleeding from bigger vessels and in patients with hypofibrinogenemia, some stages of disseminated intravascular blood coagulation.

Calcium chloride, Calcium gluconate are compounds of blood coagulation system, stimulate formation of active factors, are used for bleeding, for prophylaxis of bleeding, for increasing of capillary permeability.

Gelatina medicinalis stabilizes vascular walls, increases blood viscosity, is used for bleeding from bigger vessels (IV).

VIKASOLUM

- is indirect-acting anticoagulant, water-soluble synthetic vitamin K
- is administered orally, IM, rarely IV; therapeutic effect develops slowly and occurs in 12-18 hr
- takes part in synthesis of clotting factors in the liver
- is used for prophylaxis of bleeding, for chronic and repeated bleedings, radiation sickness, liver diseases, overdose of indirect-acting anticoagulants
- is contraindicated to patients with hypercoagulation, thrombosis, thromboembolism

TOPICALLY APPLIED PREPARATIONS FOR TERMINATION OF CAPILLARY BLEEDING IN DENTISTRY

- ✚ Thrombin (coagulant, active clotting factor)
- ✚ Spongia gelatinosa (thrombin preparation)
- ✚ Adrenalin hydrochloride (it stops capillary bleeding due to vasoconstriction)
- ✚ Adroxone (similar to adrenalin, it stops capillary bleeding due to vasoconstriction)
- ✚ Hydrogen peroxide (antiseptic, it stops capillary bleeding due to denaturation of proteins).

ANTICOAGULANTS

Classification

1. Direct-acting (are active in vivo as well as in vitro)

Heparin
Fraxiparin
Sodium citrate

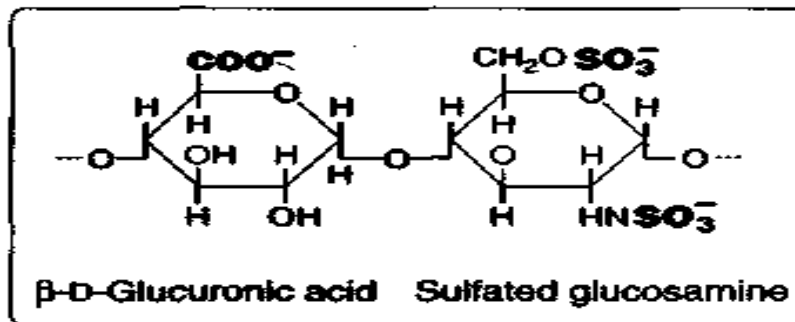
2. Indirect-acting (are active only in vivo)

Warfarin

Neodicumarinum
Phenylinum

HEPARIN

It is natural substance produced by mast cells. High concentration of heparin is observed in lungs and wall of intestine. It belongs to acidic mucopolysaccharides.



Disaccharide component of *heparin* showing negative charges due to carboxyl and sulfate groups

Pharmacokinetics

- is administered IV, IM, SC, topically
- after IV administration begins to act immediately, acts during 4-6 hr
- after IM administration begins to act after 15-30 min, acts during 6-8 hr
- after SC administration begins to act after 30-60 min, acts during 8-12 hr
- is metabolized in the liver
- is excreted with urine

Mechanism of action

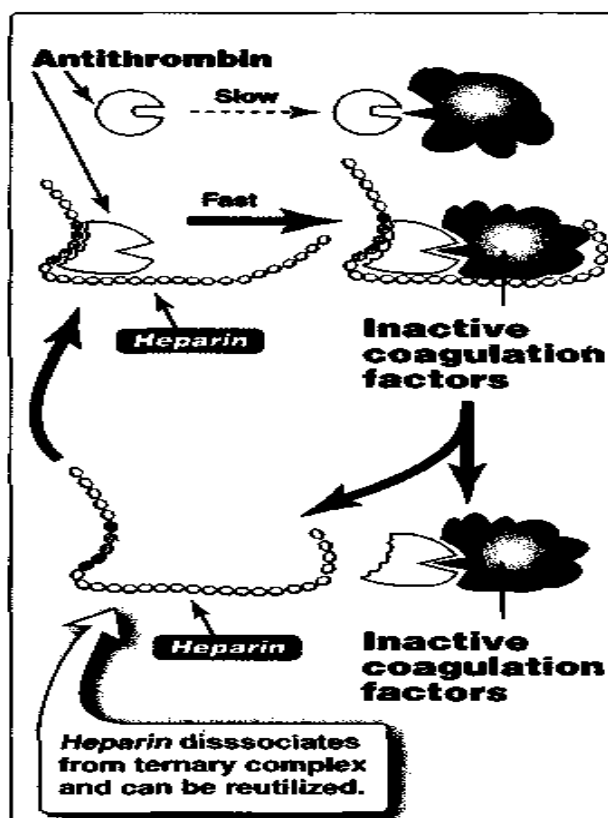
Heparin binds to anti-thrombin III" conformational change " rapid inactivation of thrombin and inhibition of fibrinogen conversion to fibrin.

Heparin has negative charge " is absorbed on blood cells " increase in negative charge of platelets " decrease in platelet aggregation and adhesion.

Heparin releases lipoprotein lipase from endothelial cells

Pharmacodynamics

- strong rapid decrease in all stages of blood coagulation
- decrease in platelet aggregation
- improve of microcirculation and coronary circulation
- decrease in lipids concentrations in blood serum
- decrease in inflammation
- decrease in immunity
- increase in synthesis of surfactant in lungs
- decrease in blood pressure (in higher doses)
- decrease in glucose level in blood serum (in higher doses)
- increase in diuresis (in higher doses)



Indications

- Acute thrombosis and thromboembolism
- Myocardial infarction
- Ischemic insult
- Prevention of thrombus formation after surgeries
- During haemodialysis or blood transfusion
- Trombophlebitis
- Syndrome of disseminated blood coagulation
- Atherosclerosis
- Autoimmune diseases
- Chronic non-specific diseases of lungs
- Paradontitis, stomatitis (topically)

The time of bleeding or the time of blood coagulation should be controlled !

Side-effects

1. Bleeding
2. Haematomes
3. Micro- and macrohaematuria
4. Thrombocytopenia
5. Allergy
6. Osteoporosis
7. Silvering of the hair

8. Bleeding gums, hematomes and petechia in mucous membrane of oral cavity

Contraindications

1. Haemorrhagias
2. Haemorrhagic diathesis
3. Leukemia
4. Anaemia
5. Malignant diseases
6. Gastric ulcer
7. Hypertention
8. Severe diseases of liver and kidney

In overdose – induce of Protamine sulfate !

FRAXIPARINE

- It is low molecular weight heparin
- is administered SC once a day; has bigger bioavailability, longer duration of action, less binding with plasma proteins
- depress activated Stuart-Prauers factor more than prothrombin
- is used for treatment of thromboflebitis, prevention of thrombus formation after surgeries.

NEODICUMARINUM

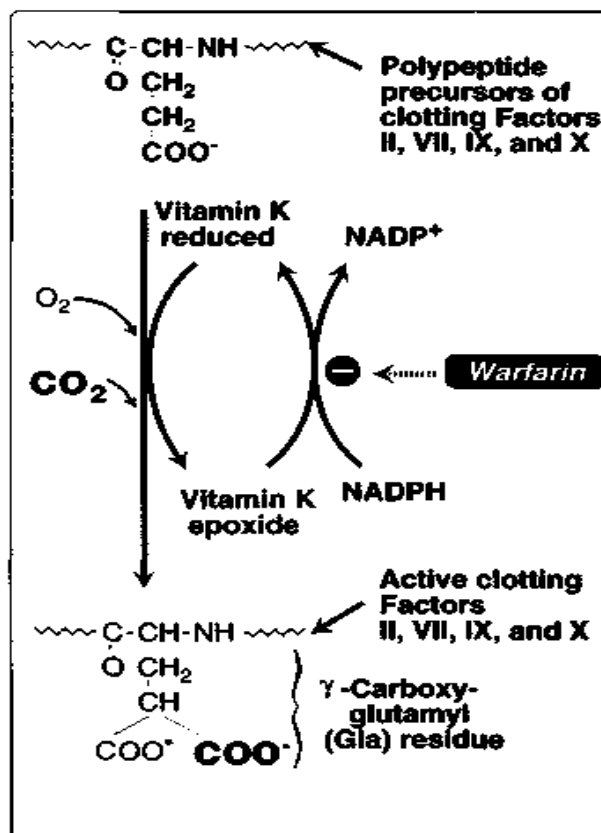
It is indirect –acting anticaagulant, coumarin derivative

Pharmacokinetics

- is administered orally
- is absorbed in GI tract
- is bound with proteins in plasma
- is metabolized in liver
- begins to act 2-3 hr after administration
- maximal action after 12-30 hr after administration
- action lasts during 48 hr after the end of treatment
- is excreted by urine

Mechanism of action

Mechanism of action of Neodicoumarinum, warfarin and other indirect-acting anticoagulants is block of epoxide reductase in the liver " block of creation of active form of vitamin K " inhibition of sdyntesdis of clotting factors.



Pharmacodynamics

- Decrease in blood coagulation
- Increase in fibrinolysis
- Decrease in lipids concentration in blood

Indications

- Acute thrombosis (together or after of heparin's usage)
- Myocardium infarction
- Ischemic insult
- Thrombo-embolism
- Thrombophlebitis
- Prevention of thrombus formation after surgeries

Index of prothrombin should be controlled !

Side-effects

1. Bleeding
2. Forming of haematomas
3. Haematuria
4. Dyspepsia
5. Oppression of liver function
6. Allergy
7. Bleeding gums, hematomas and petechia in mucous membrane of oral cavity

Contraindications

1. Haemorrhages
2. Haemorrhagic diathesis
3. Gastric ulcer
4. Malignant diseases
5. Diseases of liver and kidney
6. Pregnancy

For treatment of overdose – Vikasolum !

PHENYLINUM

- It is indirect-acting anticoagulant; indandione derivative
- mechanism of action is the same of Neodicumarinum
- start of action is slower, duration of action is more
- may cause pink color of urine resulting from excretion of drug and its metabolites.

ANTI-PLATELET DRUGS

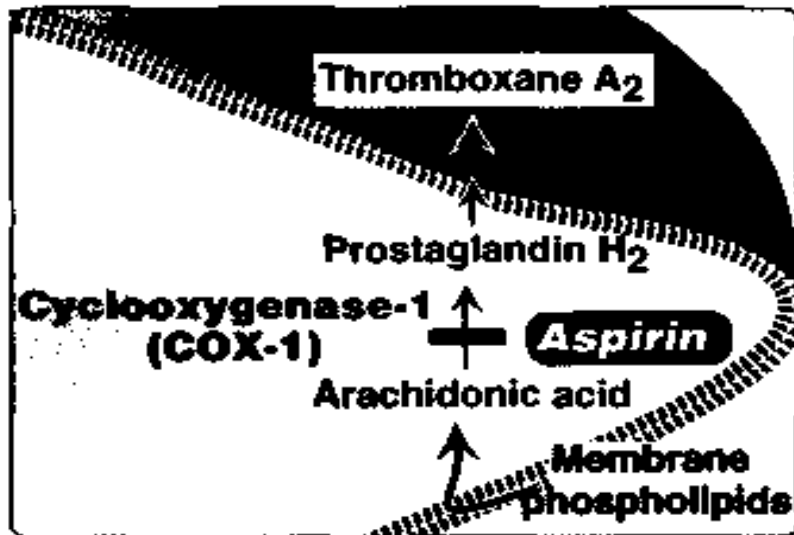
Classification

1. COX-inhibitors
Acetylsalicylic acid (Aspirin)
2. Inhibitors of phosphodiesterase
Dipyridamole
3. Inhibitors of ADP-mediated aggregation
Ticlopidine (Ticlide)

ANTI-PLATELET ACTION OF ASPIRIN

Aspirin irreversibly inhibits platelet cyclooxygenase-1" prevention of synthesis of thromboxane A₂" decrease in platelet aggregation.

This effect is occurred in lower doses (less than 0,5 per day) and lasts more than 48 hr. In higher doses aspirin also inhibits synthesis of prostacycline.

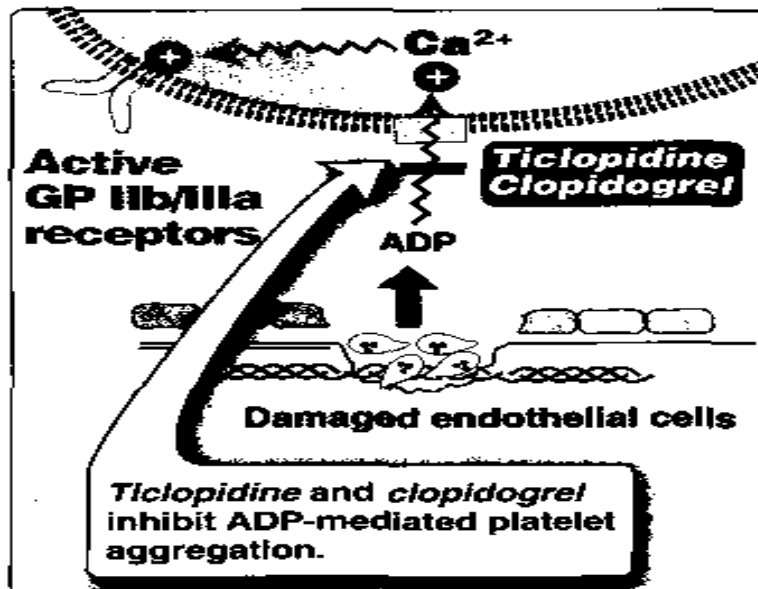


ANTI-PLATELET ACTION OF DIPYRIDAMOLE

Dipyridamole inhibits adenosine desaminase and phosphodiesterase in platelets " increase in cAMP concentration in cells " inhibition of thromboxane A₂ synthesis " decrease in platelet aggregation. It also increases prostacycline level.

ANTI-PLATELET ACTION OF TICLOPIDINE

Ticlopidine irreversibly blocks purinergic receptors for ADP in platelet membranes " inhibition of ADP-induced expression of glycoprotein (GP) IIb/ IIIa receptors in platelet membrane " decrease in platelet aggregation.



INDICATIONS TO ANTI-PLATELET DRUGS USAGE

- prevention of thrombosis and re-thrombosis (as discontinuation of anticoagulant therapy)
- prophylaxis of myocardial infarction and insult
- prophylaxis of thrombosis after surgeries
- angioplastics
- prevention of thrombosis in patients with prosthetic cardiac valves
- thrombophlebitis

DRUGS AFFECTING FIBRINOLYSIS

Classification

1. Fibrinolytic drugs
 - a) direct-acting
Fibrinolytic
 - b) indirect-acting (activators of profibrinolytic)
 - non-selective
Streptokinase
Streptolysin
 - selective
Alteplase
2. Inhibitors of fibrinolysis
 - a) direct-acting
Contrykal
 - b) indirect-acting
Aminocaproic acid
Amben

FIBRINOILYSIN

- It is protein from donors' plasma, the active factor of fibrinolysis
- is administered by IV infusion
- has direct action on fibrin and dissolves fibrin clot in the first hours after thrombosis
- is used for treatment of acute thrombosis, acute myocardial infarction, thrombophlebitis
- may cause bleeding resulting from increase in fibrinolysis, allergy, anaphylaxis, arrhythmia, hypotension
- contraindications: bleeding, cerebral vascular accident, recent trauma of brain, surgery, uncontrolled hypertension.

ACTIVATORS OF FIBRINOLYSIS

STREPTOKINASE

- It is the proteolytic enzyme from haemolytic streptococcus.
- It acts indirectly, inhibits the conversion of plasminogen to plasmin " degradation both of fibrin and fibrinogen " systemic activation of fibrinolysis and dissolving of thrombus.
- Plasma half-life is 23 min; is administered by IV infusion (intracoronary infusion in myocardial infarction).
- It is more active than fibrinolytic, does not cause arrhythmia.

ALTEPLASE (ACTILISE)

- is tissue plasminogen activator, product of biotechnology
- half-life is 5 min, is administered by IV infusion
- has high affinity for fibrin and selectively acts only on plasminogen, bound with thrombus

INHIBITORS OF FIBRINOLYSIS

CONTRICAL (Aprotinin)

- is direct acting inhibitor of fibrinolysis and proteolysis
- is administered IV slowly or by IV infusion
- binds with plasmin and inactivates it, inhibits activity of trypsin and kallikrein

- inhibits fibrinolysis and decreases bleeding caused by activation of fibrinolysis; inhibits proteolysis and inflammation
- indications: bleeding resulting from activation of proteolysis, myocardial infarction, acute pancreatitis, prophylaxis of proteolytic complications after surgeries on pancreas, thyroid glands, prevention of proteolysis activation after the surgery on bigger salivary glands; paradontitis (topically)
- side-effects: allergy, nausea, vomiting, hypotension, tachycardia

AMINOCAPROIC ACID

- is indirect-acting inhibitor of fibrinolysis
- is administered orally and by IV infusion, acts during 4-6 hr, is not metabolized and excreted with urine
- interacts with plasminogen and inhibits its transformation into plasmin, particularly inhibits plasmin; inhibits proteolytic enzymes and kallikrein
- inhibits fibrinolysis and decreases bleeding caused by the activation of fibrinolysis; oppresses proteolysis, decreases inflammation, has anti-allergic action, stimulates antitoxic function of the liver
- indications are similar to the same to contrykal and also syndrome of disseminated intravascular blood coagulation, obstetrics pathology (ablation placenta, uterine haemorrhages), liver diseases, hypoplastic anaemia
- in dentistry is applied topically to treat paradontitis and to stop bleeding from dental root channels
- side-effects: dizziness, hypotension, bradycardia, arrhythmia, skin rash, vomiting, nausea