Drugs for coagulation disorders part I

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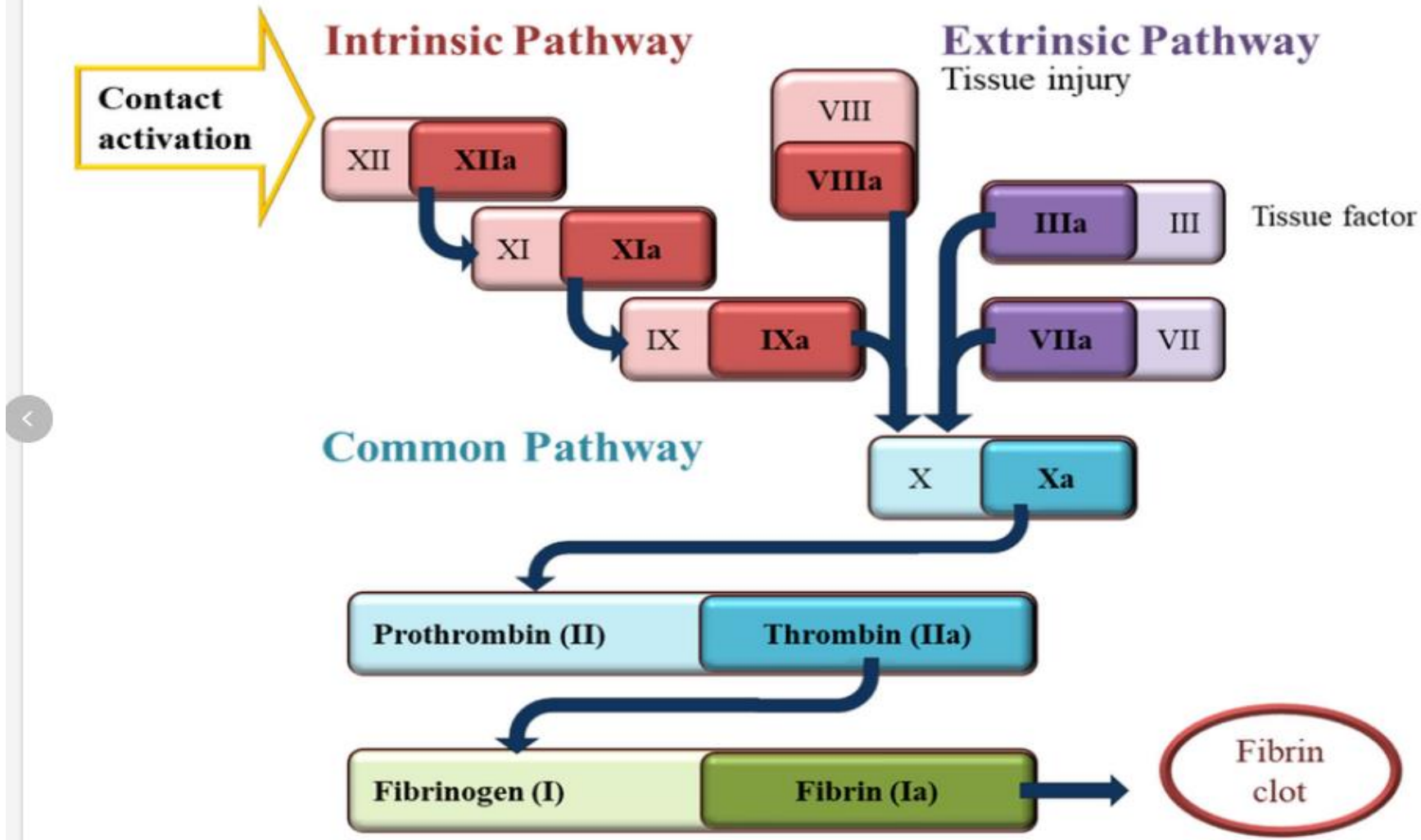
Coagulation disorders

- Coagulations disorders are **conditions that affect the blood's clotting activities.**
- **Increased coagulability**: DVT, stroke, MI, pulmonary emboli, DIC, Estrogen therapy,……
- **Bleeding disorders**: hemophilia and von Willebrand disease result when the blood lacks certain clotting factors

Thrombosis (increased coagulation)

- **Thrombi & emboli are the most common & serious abnormalities of blood disorders.**
  - ***Thrombosis*: formation of an unwanted clot within a blood vessel.**
  - ***A thrombus*: A clot that adheres to a vessel wall.**
  - ***Embolus*: is an intravascular clot that floats in the blood i.e., a detached thrombus.**
- **<u>Both thrombi and emboli are dangerous, because they may block blood vessels and deprive tissues of oxygen and nutrients.</u>**


Intrinsic Pathway
Extrinsic Pathway
Tissue injury
Contact activation
XII
XIIa
VIII
VIIIa
XI
XIa
IIIa
III
Tissue factor
IX
IXa
VIIa
VII
Common Pathway
X
Xa
Prothrombin (II)
Thrombin (IIa)
Fibrinogen (I)
Fibrin (Ia)
Fibrin clot

Anticoagulants

1. **Indirect thrombin inhibitors:**

a) Heparins (unfractionated heparin 'UFH' & Low molecular weight heparin "LMW") .

b) Synthetic pentasaccharide: e.g., fondaparinux.

2. Vitamin K antagonist : e.g., Warfarin.

3. **Direct thrombin inhibitors :** e.g., Argatroban, Dabigatran

4. **Direct factor Xa inhibitors:** e.g., Betrixaban, rivaroxaban

1- INDIRECT THROMBIN INHIBITORS

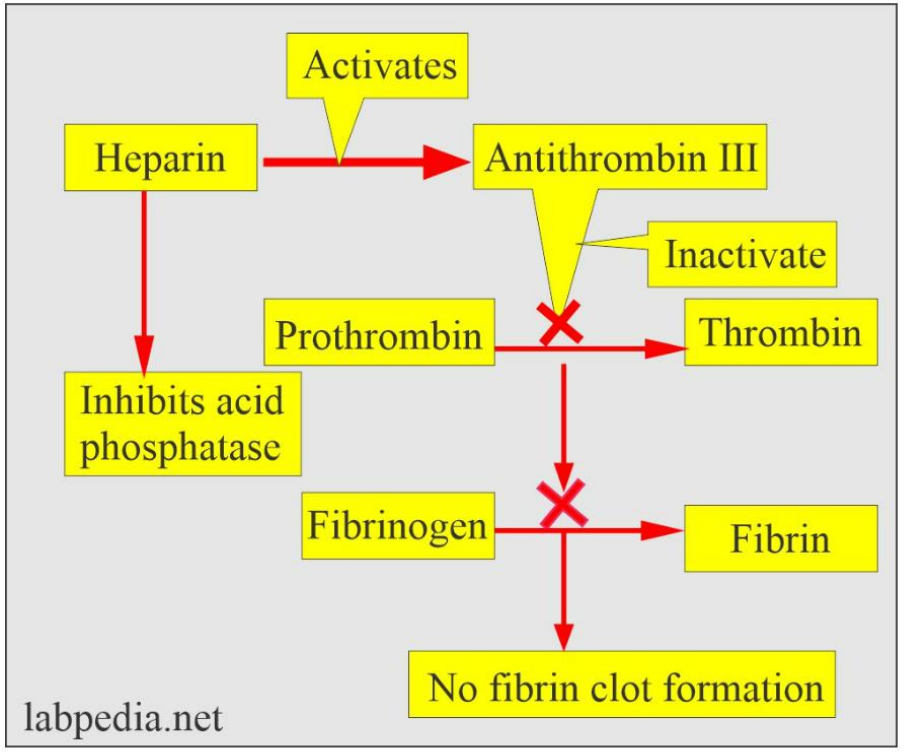
A) Unfractionated Heparin (UFH) (Heparin) :

Pharmacokinetics of Heparin:

* **Due to highly negative charge (ionized) of heparin and its large molecular size, it is not given orally. It is given parenterally**
* **I.V.** →immediate onset of action (5 hours duration) -in emergency
* **S.C.** → delayed onset (1-2h) but for long-term maintenance.
* **I.M. injection must be avoided (cause painful hematomas).**
* **Half life:** 1-1.5 H (short acting)
* **NOT Passing BBB and placenta**
* **Elimination: liver and kidney**

Mechanism of action of heparin

- **Heparin**, **LMWHs**, and **fondaparinux** have **no intrinsic anticoagulant activity**.
- These agents **bind to antithrombin-III (protease)**: naturally occurring inhibitor of clotting factors: **2**, 9,**10**, 11, 12.
- **Heparin inhibits both thrombin and factor Xa equally.**
- **Factor Xa inhibition is more specific than thrombin inhibition**.
- **Fondaparinux**: **has only antifactor Xa activity**



Heparin mode of action

Monitoring of Anticoagulant Therapy

- Monitoring of **aPTT (activated partial thromboplastin time)** is necessary in case of heparin administration either S.C. or I.V. (Very important in I.V.).

- **Therapeutic goal:** aPTT should be **1.5-2.5 times normal** control value.
- Normal aPTT: 30-40 sec.
- aPTT in heparin therapy: 60-100 sec.

Adverse Effects of Unfractionated Heparin

1. **Bleeding:**

- **Dose-dependent & dosage adjustment based on aPTT monitoring reduces the incidence of bleeding.**

- **Protamine sulfate** (a mixture of basic **(positively charged)** polypeptides isolated from salmon sperm) is used to overcome bleeding because it binds tightly **(electrostatic bond)** to heparin and neutralizes its anticoagulant effect.

- **Dose** : (1 mg protamine/100 units heparin) required to neutralize the heparin present in the plasma.

N.B. Protamine binds only long heparin molecules. Therefore, protamine **only partially** reverses the anticoagulant activity of LMWHs and **has no effect on that of fondaparinux**.

2. **Heparin-Induced Thrombocytopenia (HIT- immune-based reactions):**

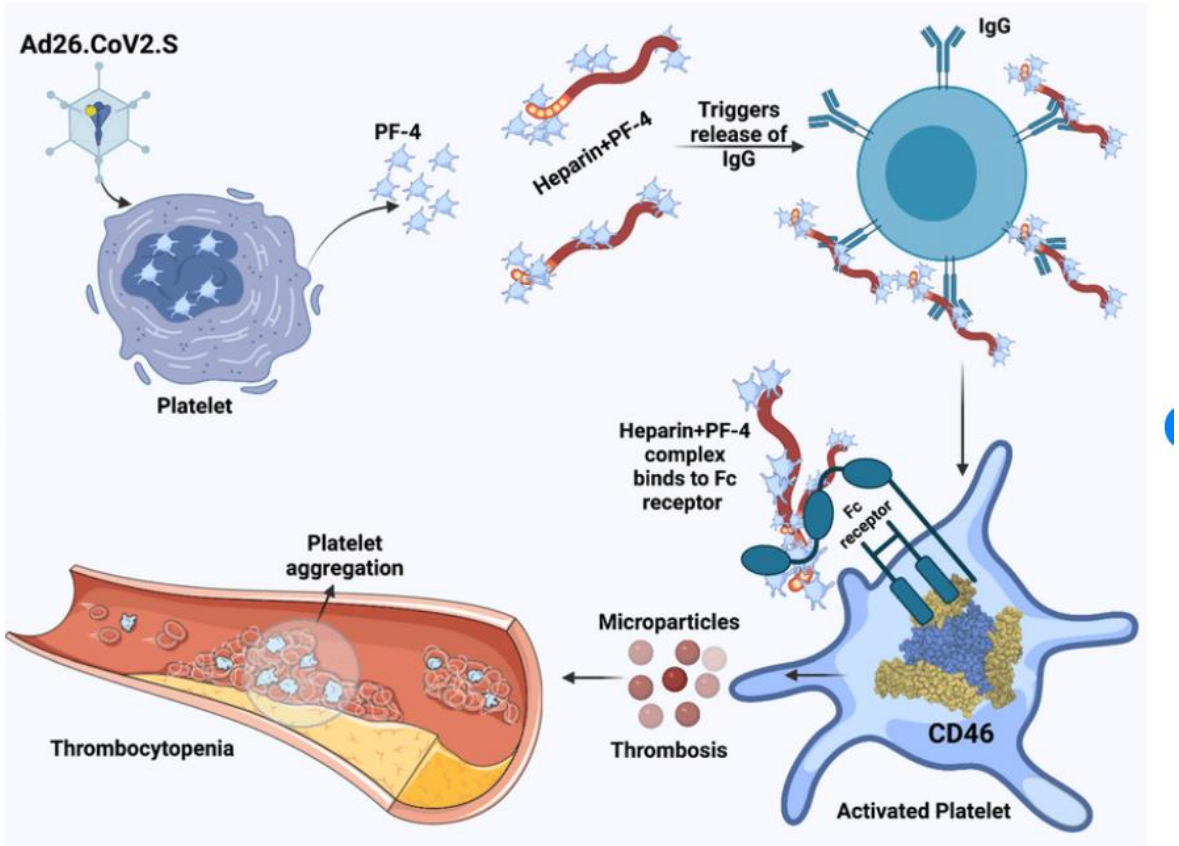
- **in about 0.5 % of patients after 5 days of starting drug therapy.**
- **<u>Management</u>: heparin must be stopped, and the patient must be given alternative anticoagulant.**

3. Osteoporosis

4. Alopecia

5. Hypersensitivity

6. Muscle hematoma if given IM



B) Low Molecular Weight Heparins (LMWH)

- **Enoxaparin (Clexane), Dalteparin (fragmin)**
- **Fragments of unfractionated heparin which composed of shorter polysaccharide chains with average MW about 5000 d.**
- **Affect only factor Xa: less risk for thrombocytopenia and less osteoporosis**
- **Longer duration of action: 24 H: single daily dose**

C) Fondaparinux , Rivaroxaban (oral)

- **Administered by S.C. injection, single daily dose without coagulation monitoring.**
- **Specific for factor Xa inhibition**
- **Advantages**: Fondaparinux appears to be much less likely than heparin or LMWH to trigger the syndrome of heparin-induced thrombocytopenia.
- **Indications**: **only injection**
- 1- Thromboprophylaxis in patients undergoing hip or knee surgery
- 2- Initial therapy in patients with pulmonary embolism or DVT.

Pharmacological properties of Low Molecular Weight Heparins (LMWH)

Enoxaparin (Clexan; S.C.), dalteparin: they differ from heparin in:

1. They are **fragments** of unfractionated heparin with **low molecular weight**.
2. Promote inhibition of **factor Xa** by antithrombin with little effect on thrombin.
3. Have **longer t½** , so they are used S.C. once / day.
4. They have **high bioavailability and predictable anticoagulant effect**, so no need for routine lab monitoring or dose adjustment.
5. They have **lesser side effects** as thrombocytopenia, osteoporosis and bleeding.
6. Their effect is **incompletely** neutralized by protamine sulphate.
7. They are **monitored by antifactor Xa activity** but not by aPTT.

Indications of Heparins and its derivatives:

* **Treatment of thromboembolic disorders:**
  - **First choice because of its rapid onset of action.**
  - **Used for 4-5 days followed by oral anticoagulant warfarin:**
    - **a)Deep venous thrombosis (DVT)**
    - **b)Pulmonary embolism (PE)**
    - **c)Primary prophylaxis of DVT or PE**
* **Prevention of venous thromboembolism in high risk patients: After orthopedic (hip or knee surgery) or gynecological surgery.**
* **Initial management of :**
  - **a)Unstable angina and atrial fibrillation & in mitral valve disease, especially with atrial fibrillation.**
  - **b)During and after cardiac surgery e.g., Prosthetic heart valves, coronary angioplasty or stent placement, cardiopulmonary bypass grafts.**
  - **c)Transient ischemic attacks (TIA) or Cerebral infarction.**
  - **d)In disseminated intravascular coagulation (DIC)**
* **DVT during pregnancy.**
- **To prevent occlusion of hemodialysis machine.**

2- Oral anticoagulants

Warfarin sodium (Dendivan or marivan ®)

* **Prototype of cumarine anticoagulants (synthetic)** and **effective only in vivo**.

Mechanism of action:

* **Vit K antagonist** : **inhibits the enzyme Vit k epoxide reductase** which is responsible for the production and activation of vit k-dependent coagulation factors (II, VII, IX, and X) by the liver.
* Slow onset of action because its effect is dependent on the $t_{1/2}$ of these factors (from 5-100 hours).
* So,
* **(heparin + warfarin)** must be given for first 4-5 days followed by warfarin alone.

Pharmacokinetics of Warfarin:

* **Taken only orally. No more benefits from parenteral administration. Its oral bioavailability is very high.**
* **Plasma Protein Binding: about 99%.**
* **Metabolized into inactive metabolites by the liver.**
* **$t_{1/2}$ = 40 hours & duration of action = 2-5 days.**
* **Enterohepatic circulation accounts for long half-life.**
* **Inactive metabolites are excreted by the kidneys.**

Administration of warfarin:

- **It is given orally.**
- **Dosage adjustment based on prothrombin time (PT) (INR: International Normalized Ratio) monitoring: should be twice the control (INR= 1-1.5).**

Conditions that affect warfarin activity

❑ Factors that decrease warfarin effectiveness:

* **Cholestyramine** inhibits warfarin absorption.
* **Genetic resistance to vit K epoxide reductase**.
* ↑ **metabolic clearance of warfarin** by **enzyme inducers** (phenobarbitone, rifampicine, phenytoin and chronic alcohol ingestion.

❑ Factors that increase warfarin effectiveness:

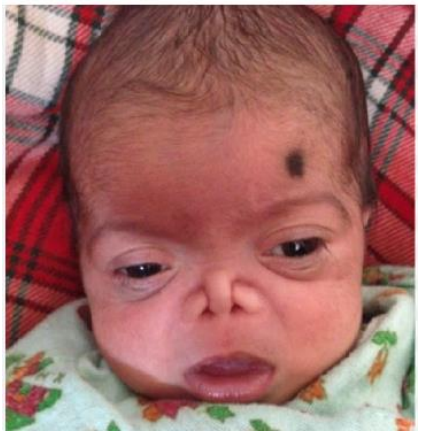
* ↓ **vit k** due to damage of intestinal flora by **broad spectrum antimicrobial agents.**
* ↑ **displacement of warfarin from plasma protein binding by NSAIDs**.
* ↓ metabolism of warfarin by **enzyme inhibitors** (metronidazole, cimetidine, allopurinol, amiodarone and acute ingestion of alcohol

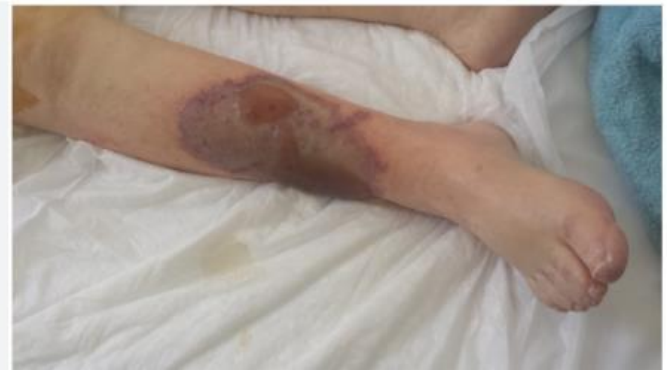
Adverse effects and toxicity of warfarin:

1. **Bleeding: antidote: by vit K1.: 3-5 mg IV**
2. **Infrequent skin reactions (hemorrhagic skin necrosis, purple toe syndrome, alopecia, urticaria and dermatitis).**
3. **Abortion, birth defects and intrauterine fetal death, CNS hemorrhage. Therefore, it must be avoided during pregnancy. (teratogenic): fetal warfarin syndrome**
4. **Osteoporosis.**
5. **Sudden withdrawal: rebound synthesis vitamen K- dependent clotting factors: thrombosis**

Indications of warfarin:

1. **Prevention of DVT or pulmonary embolism recurrence following initiation course of heparin.**
2. **Prevention of venous thromboembolism in high risk patients after orthopedic (hip or knee surgery) or gynecological surgery.**





Other New Parenteral Anticoagulants (Thrombin inhibitors)

1. **Lepirudin:** is a direct thrombin inhibitor and approved I.V. for treatment of patients with heparin-induced thrombocytopenia. There is no antidote for lepirudin.
2. **bivalirudin :** administered I.V. and is used as an alternative to heparin in patients undergoing coronary angioplasty or cardiopulmonary bypass surgery. The $t_{1/2}$ of bivalirudin is 25 min.
3. **Argatroban**
4. **antithrombin** is a recombinant form of human antithrombin produced from the milk of genetically modified goats. It is approved as an anticoagulant for patients with hereditary antithrombin deficiency undergoing surgical procedures.

New oral anticoagulants

1. Dabigatran: Direct thrombin inhibitors

- It is prodrug and approved for stroke prevention in patients with atrial fibrillation.
- ***Direct thrombin inhibitor*** **with high affinity and specificity.**
- **Half-life: 12–14 hours**
- It produces predictable anticoagulant response and so routine coagulation monitoring is unnecessary.
- **It is more safe and more effective than warfarin.**
- **Dabigatran antidote is recently available (idarucizumab)**

2. Betrixaban:

*** Direct factor Xa inhibitor**

*** Safe and well tolerated.**

- **It is The only [anticoagulant] that is not cleared by the kidneys and so no dose adjustment in renal impairment.**

Contraindications of anticoagulants

- 1- Patients with hypersensitivity to the drug
- 2- Active bleeding and hemophilia
- 3- Significant thrombocytopenia (platelet count is necessary)
- 4- Visceral carcinoma
- 5- Uncontrolled hypertension & intracranial hemorrhage
- 6- Advanced hepatic or renal disease.
- 7- Active tuberculosis & ulcerative lesions of the gastrointestinal tract.
- 8- Patients who have recently had surgery of the brain, spinal cord, or eye

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Thank you