HEMATOPOIETIC & LYMPHATIC SYSTEM

-HAYAT BATCH-

SUBJECT : Pharma

LEC NO. : 4

DONE BY : Abd

وَقُل رَّبِّ زِدْنِي عِلْمًا

6. **Prasugrel: (oral)**
   - Increased risk of bleeding (CI: in patients with history of TIA or stroke) bleeding stroke
7. **Clopidogrel (oral once /day)** (preferred to ticlopidine; less risk of neutropenia)
   - Rash - Gastric irritation- diarrhea.
   - Clopidogrel is a prodrug → avoid with PPIs e.g. omeprazole as it inhibits its activation in liver by CYP450

protein pump inhibitors

8. **Ticagrelor:** shortness of breath
9. **Abciximab (IVI)**: thrombocytopenia, arrhythmia.

ANTICOAGULANTS

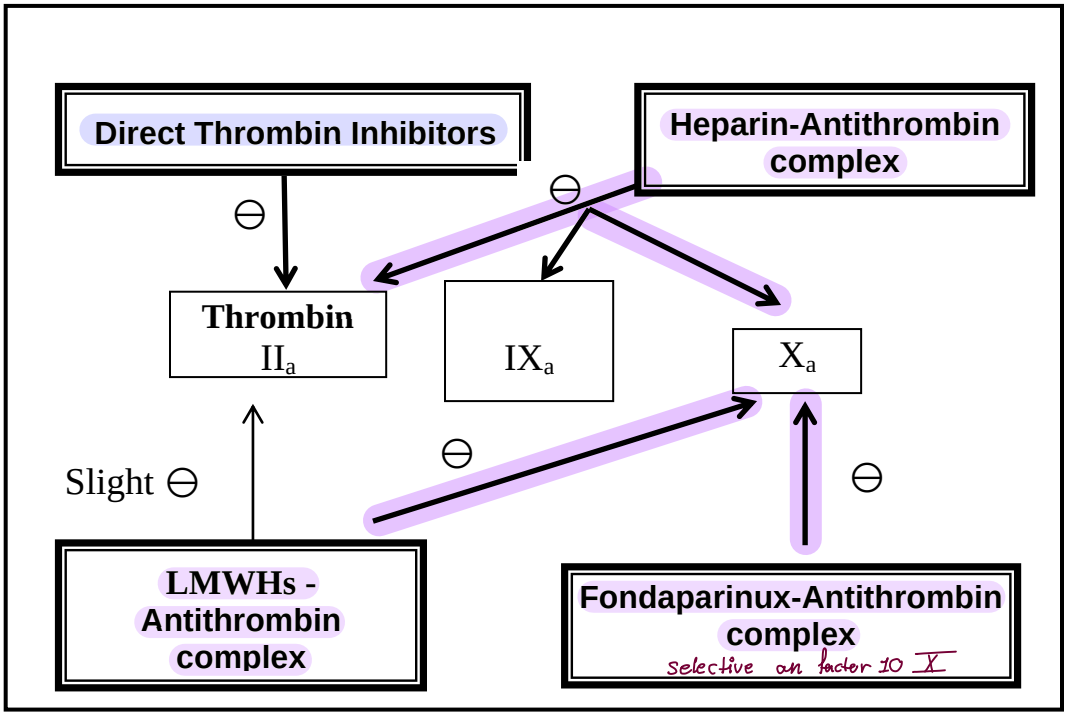
A. Parenteral Anticoagulants:

I. Indirect thrombin inhibitors: Heparin - low molecular weight heparins (LMWHs) - fondaparinux.

II. Direct thrombin inhibitors: Bivalirudin - Argatroban.

B. Oral anticoagulants: Warfarin – New oral anticoagulants (NOAC).

A.PARENTERAL ANTICOAGULANTS



Site of action of Indirect & Direct Thrombin Inhibitors

→ Indirect Thrombin inhibitors: ① Heparin ② LMWH ③ fondaparinux
These form a complex with antithrombin & may work on other factors.

→ Antithrombin is one of those are indogenous substances that keeps blood in it's fluid state.
indogenous anti-coagulants

I. Indirect thrombin inhibitors:

1. Heparin (unfractionated heparin; UFH)

↳ Didn't undergo any processing « taKen from it source as it's »

Chemistry

- Sulfated mucopolysaccharide with high MW **(HMWH)** «High molecular weight heparin»
- Highly acidic with electronegative charge.
- Source: porcine (pigs) intestinal mucosa and bovine (goats) lung

As both sources are animal sources this may « induce allergic reaction »

→ Note that : for a drug to optimally absorbed it must be both water & Lipid soluble.
↳ Heparin doesn't follow this role as it's highly ionized « poor oral absorption ».
↳ Heparin must be given Parenterally

Pharmacological Actions

1. Anticoagulant action: (effective both *in vitro* and *in vivo*)

   Mechanism: combines with antithrombin (natural anticoagulant factor) forming heparin-antithrombin complex which accelerates the inhibitory effect of antithrombin on activated clotting factors specially:

   - Factor IIa (Thrombin) - factor IXa - factor Xa. (192) active
2. Slight vasodilator effect → canalization of thrombus.
3. Plasma-clearing effect by stimulating lipoprotein lipase enzyme.

Pharmacokinetics

- Immediate onset of action after IV injection and short duration (4-6 h).
  ↳ thus given by infusion
- 80 % metabolized in the liver by heparinase enzyme.
- 20 % excreted unchanged via the kidney.
- Does not cross placenta & is not secreted in milk (high MW) → can be used during pregnancy (if clearly indicated) or lactation.

Routes of Administration & Doses

«international unit» « Hospitalized patients »

- **IV bolus** (5,000 IU), followed by **IV infusion** (1,000 IU/h); guided by aPTT).
- **SC**: 5,000 IU (low dose of heparin) for prophylaxis, 2 hours preoperative and every 12 hours postoperative for 5-7 days.

Heparin should not be given by IMI as hematoma can occur.

↳ bleeding under the skin

Control of Therapy → used to monitor the unpredictable kinetics & dynamics

- **aPTT** (activated partial thromboplastin time): should **Not > 2-2.5** normal value (normal value 30-35 seconds).

Adverse Effects

1. **H**emorrhage.
2. **H**air loss (alopecia). unknown mechanism (reversible)
3. **H**ematoma if given by IMI. As it's anticoagulant needle puncture will cause constant bleeding
4. **H**ypersensitivity. As it's from non-human source
5. **H**yperkalemia (monitor K level if heparin is given > 7 days)
   2ry to aldosterone deficiency (due to ② inhibition of an enzyme necessary for aldosterone synthesis (Angiostensin) OR ① block of Ag-II receptors in suprarenal cortex)
   Aldosterone is a hormone secreted from adrenal gland of Kidneys it causes Na^+ retention thus ↑ blood volume & pressure on the other hand aldosterone deficiancy ↑ Na^+ in urine thus K^+ ↑ in blood
6. Osteoporosis (on long term use, specially in pregnancy). «bone weakness»
7. Heparin-induced thrombocytopenia (HIT): (regular platelet count is required):
   a) Early: mild due to direct effect on platelets.
   b) Late: severe due to immunoglobulin-induced platelet aggregation. (Decrease)

   in some cases heparin may cause thrombus so you have to
   ttt: Replace heparin by direct thrombin inhibitor or fondaparinux
8. Unpredictable pharmacokinetic & pharmacodynamic properties: (because it binds to plasma proteins, macrophages, platelets or endothelial cells)
   ↳ As the amounts of heparin binding to these blood components varys btwn people

   ↑ The way it reacts in the body is unpredictable it doesn't alway work in the most ideal way mostly via SC route

Reversal of Heparin toxicity

- **Stop Heparin - Fresh blood transfusion** (As coagulation factors still working)
- Give heparin **antidote**: **Protamine sulfate** (chemical antagonism)
  - Highly basic with low MW carrying electropositive charge.
  - Neutralizes heparin (each **1** mg neutralizes ≈ **100** IU heparin, **Not exceed 50 mg** in any **10 min** period).
  - **Avoid overdose →** Has a slight anticoagulant effect.
  - Partially antagonizes Low-Molecular-Weight Heparins.
  - Does not antagonize fondaparinux.

2. Low-Molecular-Weight Heparins (LMWHs):

(Dalteparin - Enoxaparin -Tinzaparin)

- They are fractions of the standard heparin (unfractionated heparin) thus they have a low molecular weight.
- They are mostly given subcutaneously.
- Mainly renal excretion. "good for people with liver diseases"

Mechanism of Action

- They bind to antithrombin increasing its inhibitory effect on factor $\mathbf{X_a}$ and to a lesser extent on thrombin (Factor II_a).

Advantages of LMWHs

1. Equal efficacy to unfractionated heparin.
2. Greater bioavailability from sc sites.
3. Long $t_{1/2}$ ➔ given subcutaneously once or twice/day.
4. Less thrombocytopenia & osteoporosis.
5. Less risk of bleeding.
6. No need for laboratory monitoring (predictable ph.kinetics & dynamics).

3. Indirect selective inhibitor of factor Xa: Fondaparinux

- Synthetic Pentasaccharide (5 carbons) molecule, derivative of heparin
- Binds to antithrombin with ➔ efficient inactivation of factor Xa.
- Long $t_{1/2}$ ➔ given once daily sc.
- Low risk of HIT
- Used in venous thromboembolism & heparin - induced thrombocytopenia. ("As an alternative")
- Bleeding is the major adverse effect: not antagonized by protamine sulfate.
- Requires less monitoring than heparin (predictable ph.kinetics & dynamics)

II. Parenteral Direct Thrombin Inhibitors: (DTIs)

- Directly bind to thrombin independent of antithrombin ➔ more inhibition of fibrin-bound thrombin.
- Given intravenously and Sc.
- Bleeding is the major adverse effect (NO antidote)
- Used in: - Percutaneous intervention (PCI) & Coronary angioplasty (قسطرة عن طريق الجلد، توسيع الشريان التاجي)
  - Patients with HIT

Argatroban

- Preferred in patients with renal insufficiency (cleared hepatically not renally).

Bivalirudin (hirudin analogue)

- Also inhibits platelet activation.