Anti-Coagulants

Parenteral Anticoagulants :

UFH (unfractionated heparin) : high molecular weight :3000-30000 .

MOA : Inactivation of coagulation factors : XIIa, XIa, IXa, Xa, IIa

Lower Molecular Weight Heparin < 8000 : works more on inhibiting activated factor 10.

Enoxaparin – Lovenox - Dalteparin

Direct Thrombin : it works specifically on thrombin.

Reversible : Bivaluridin – Argatroban - Dabigatran

irreversible : Lepirudin

Activated factor 10 inhibitors : only works on activated factor 10

Indirect Is :Fondaparinux

Direct Is: Rivaroxaban

N.B: Rivaroxaban and Dabigatran can be given orally

Pharmacokinetics :

- Rapid
- Variable response. Monitor by aPTT (Activated partial thromboplastin time) (1.5 - 2.5 times normal [30sec]) Or CT(clotting time) (2-3 times normal [5-7 min)
- Antidote; Protamine Sulphate IV → 1mg / 100 units UFH + Fresh blood

Oral Anticoagulants: Vit. K antagonists

MOA : Decrease Synthesis of II, VII, IX & X by by inhibiting Vit K epoxide reductase

Pharmacokinetics :

- Slow / Latency .
- Variable . Monitor by PT (2 times) . INR (2.5)

Coumarins; Warfarin – Dicumarol. (Warfarin > 40 times potency than Dicumarol)

Antidote; Vit. K1 infusion + Fresh blood + Needs de novo synthesis

LIMITATIONS

- Wide variation in drug response → a necessity for continuous monitoring (PT) & dose adjustment.
- Has narrow therapeutic window; high PPB (plasma protein bounding) & action depends on very small fraction of free drug. So any change in that level can be hazardous.
- Slow onset of action, so not in given in emergency conditions
- Has latency in its action → presents the time needed to launch new biologically inactive coagulation factors
- -Common genetic polymorphisms in CYT P450 isoforms that metabolizes warfarin → adds to its non predictable response → liability to toxicities or under use.
- Numerous food- & drug-drug interactions → liability to toxicities or under use.
- Contraindicated in some conditions liable to develop thrombosis i.e. as in pregnancy (Category X) → give heparin or LMWH instead

UFH limitations:

-No predictable anticoagulant effects; inter-patient & intra-patient variability in response to a given dosage → *in hospital setting, repeated monitoring*

-Low bioavailability → *binds to* plasma proteins, endothelium & macrophages

-Re-thrombosis → *activates platelets as it does not neutralize fibrin-bound II a*

-Heparin Induced Thrombocytopenia (HIT); in 4% pts. on heparin, latency 5-10 dys. after 1st exposure or 2-3 days. after re-exposures →Venous > Arterial thrombosis

LMWH benefits

- ↑ Predictability of anticoagulant response i.e. little inter-patient and intra-patient variability in response to a given dosage. So → effective anticoagulant activity can be achieved by calculating dosages based on body weight without the need for laboratory monitoring
- ↑ Bioavailability; as it hardly binds to plasma proteins, endothelium & macrophages
- ↓Incidence of thrombocytopenia; as it seldom sensitive to PF4
- ↓Incidence of bleeding tendency; ↓ effect AT III (anti thrombin 3) & ↓ platelet interactions
- Much better tolerability;
  - Given subcutaneously.
  - ↓ frequency of administration due to longer duration of action .
  - ↓ need for regular monitoring. Outside hospital settings

Managing HIT

- ✶ Heparin discontinuation
- ✶ No packed platelets → More thrombosis
- ✶ No warfarin → ppt .venous gangrene
- ✶ Give → DTIs (Direct thrombin inhibitors)

Drugs modulating response to VKAs :

Notes:

-Heparin and LMWH(low-molecular weight heparin) affect factor 12a ,11a ,9a, 10a , thrombin. They are monitored by APTT

-factor 10a inhibitors affects factor10a , monitored by PTT

-Direct thrombin inhibitors affect fibrin bound thrombin , monitored by APTT

-Vitamin K Antagonists (warfarin) affects on the factors that depend on vit k which are 7a , 9 a , 10 a , thrombin. Monitored by PT

-Anti thrombin 3 naturally produced from tissues inhibits activated factors 9, 10, and 2. Heparin activates it up to 1000 times

Drugs that increase toxicity (bleeding):

- Inhibition of Vit. K synthesis by intestinal flora; oral antibiotics
- Inhibition of Vit K absorption; liquid paraffin
- Decrease in drug metabolism by microsomal enzyme inhibitors; chloramphenicol, & cimetidine
- Displacment of the drug from protein binding sites; phenylbutazone,, clofibrate & salicylates
- Co-administration of drugs that increase bleeding tendency by; inhibiting platelet function; NSAID & inhibiting coagulation factors; heparin & antimetabolite

Drugs that reduce efficacy (thrombosis)

- Inhibition of drug absorption from GIT; cholystyramine, colestipol
- Increase in synthesis of clotting factors; Vit K, oral contraceptives
- Increase in drug metabolism by microsomal enzyme inducers; barbiturates, rifampicin & griseofulvin

Summary

- **Anticoagulants are mainly used in treatment of venous thromboembolism** while antiplatelets used mainly in treatment of **arterial thrombosis.**

- **Heparin :** inactivate factors **12a ,11a ,9a, 10a , thrombin**, and has a variable response monitored by PTT or APPT.
  - If there is toxicity → Antidote; **Protamine Sulphate** IV➔ Img / 100 units UFH + Fresh blood
  - It does not inhibit the fibrin bound thrombin that's why it has an incidence of causing re thrombosis.
  - It also causes Heparin Induced Thrombocytopenia (HIT); latency 5-10 dys. after 1st exposure or 2-3 dys After re-exposures **if this occurs:** Heparin withdrawn and **give DTIs** .No packed platelets or warfarin.

- **Lower molecular weight heparin** works more on inhibiting activated **factor 10**.It has ↑ Predictability of anticoagulant response , ↑ Bioavailability , ↓Incidence of thrombocytopenia ,↓Incidence of bleeding tendency and better tolerability than UFH

- **Direct factor 10a inhibitors** affects factor10a , monitored by APTT or PPT (they are the same)

- **Direct thrombin inhibitors** affect fibrin bound thrombin , monitored by PTT. It is the only drug that doesn't cause re thrombosis.

- **Vitamin K Antagonists (warfarin)** affects on the factors that depend on vit k which are **7a , 9 a , 10 a , thrombin** by inhibiting **Vit K epoxide reductase**. Monitored by PT due to its variable response.
  - Contraindicated in pregnancy ➔ give heparin or LMWH instead
  - Slow onset of action, so not in given in emergency conditions
  - Metabolize in the liver by CYT P450 → Numerous food- & drug-drug interactions.

- **Heparin** inhibit activated **factor 10 and thrombin equally,** however it **does not** inhibit the **fibrin bound thrombin** that's why it has an incidence of causing **re thrombosis.**
- **Low molecular weight heparin** works more on inhibiting **activated factor 10 more than thrombin.**
- **Activated 10 inhibitors** only works on **activated factor 10** either directly or indirectly.
- **Direct thrombin inhibitors** works only on the **fibrin bound thrombin**. That's why it is the only drug that doesn't cause **re thrombosis.**