PHARMACOLOGY

TEAM 432

Anti-Coagulant Drugs

Objectives

Re-visit the coagulation cascade
Classify drugs acting as anticoagulants
Elaborate on their mechanism of action, correlating that with methods of monitoring
Contrast the limitations & benefits of injectable anticoagulants in clinical settings
Emphasis on the limitations of VKAs & on variables altering or modifying their response
Apply such variability in a clinical scenario.

Color Guide

Slides = Black
Females slides = Green
Males slides= Blue
Explanation=Orange

Cases and Questions are very important

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Anti-Coagulant Drugs

Oral

- Vitamin K Antagonists
- Warfarin
- Dicumarol

Parental

- Heparin &UF Heparin
- Direct Thrombin Inhibitors
- Factor Xa Inhibitors
- LMWH

Intrinsic Pathway	Extrinsic Pathway
Clotting is slower	Clotting is rapid in seconds
accessed by aPTT "activated partial thromboplastin time"	accessed by PT "Prothrombin time"
Initiated by blood vessel injury	Initiated by any injury to the tissue "tissue factor"
Final common pathway	

For this coagulation, normally we have Anti-coagulant effect "anti-thrombin III" which normally inhibit these pathways and we do not get diseases and works especially on factor 8 ,10,and activated thrombin
Clinically : we have a drug "heparin" that has similar action but more potent.
It acts like and activates anti thrombin
Anti-coagulant used more for venous thrombosis
Anti-platelet used more for arterial thrombosis

If it's ER condition give parentally cuz orally will take at least 3 days to work

	PARENTAL	ORAL
Pharmacology	Clotting is rapid and variable monitor by aPTT ***(1.5 - 2.5 times)*** ***Or CT(2-3 times normal in 5-7 min)*** Inactivation of Coagulation Factors by Anti-thrombin III	Clotting is slow and variable Monitor by PT(2times) & INR(2.5) Needs de novo synthesis
Act on Factors	XIIa, XIa, IXa, Xa, IIa	decreases synthesis of II, VII, IX & X factors .
Antidote	Protamine Sulphate IV>> 1mg/1000 units UFH+/ fresh blood transfusion.	Vit. K_1 infusion+/fresh blood transfusion
Drugs	***Unfractionated heparin (mechanism of the above)***	****Vitamin K Antagonists(for above)***
Other drugs	****LMWH : more effective on F.Xa*** **Enoxaparin, Lovenox & Dalteparin** ****Direct Thrombin Inhibitors: more effective on F.IIa*** **Bivaluridin , Lepirudin & Argatroban** ****Factor Xa Inhibitors: more effective on F.Xa*** **Fondaparinux *(indirect)***	Coumarins; **Warfarin** > 40 times potency than **Dicumarol** ***Other drugs:*** ****Dabigatran:*** derivative of "direct Th. Inhibitors"but taken orally ****Rivaroxaban:*** derivative of "F.

<1.5 less efficacy, more than 2.5>> bleeding

<2 (less efficacy ,>2.5 (Bleeding

Once bleeding 0ccurs (.2.5)

The Group of drug	Activity	Monitored by
UFH	Equal effect on IIa & Xa **(IIa = Xa)**	aPTT
LMWH	***(Xa > IIa) act on factor ten more than thrombin***	Plasma F. Xa
Factor Xa Inhibitors	No effect on IIa (indirect via ATIII), and direct action	Plasma F. Xa
Direct Thrombin Inhibitors	No effect on Xa **Block thrombin only (can block the active fibrin bound thrombin site**	aPTT

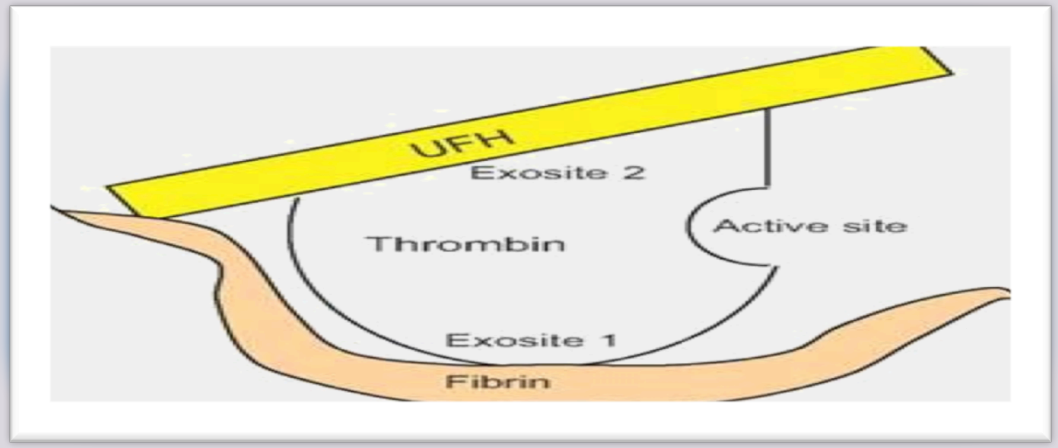
Both **UFH & LMWH** have a **re-thrombotic action**, because it leave an active site at {the Fibrin-Bundle IIa} (they only block one active site of thrombin & leave the other active site opened)

limitation of unfractionated heparin (UFH)

No predictable anticoagulant effects(can't judge its accuracy) ; variability in response to the given does from patient to other . (Given *in hospital setting, repeated monitoring)*

Low bioavailability ➔*(binds to* plasma proteins, endothelium & macrophages).

Patient may develop Re-thrombosis within 1-2 days after exposure to heparin **)** ➔ ***activates platelets & it does not neutralize fibrin-bound II a*** **(No effect on Fibrin-bound IIa)**



No packed platelets ➔ More thrombosis
No warfarin ➔ ppt .venous gangrene
Give ➔ DTIs
It works on platelates inducing thrmbocytopenia(majority) , the remaning of the plaetlates are very active that they cause thrombosis

Heparin Induced Thrombocytopenia (HIT) within 7 -10 days ; The result can be a deep vein thrombosis , we must stop heparin and give them direct thrombin inhibitors

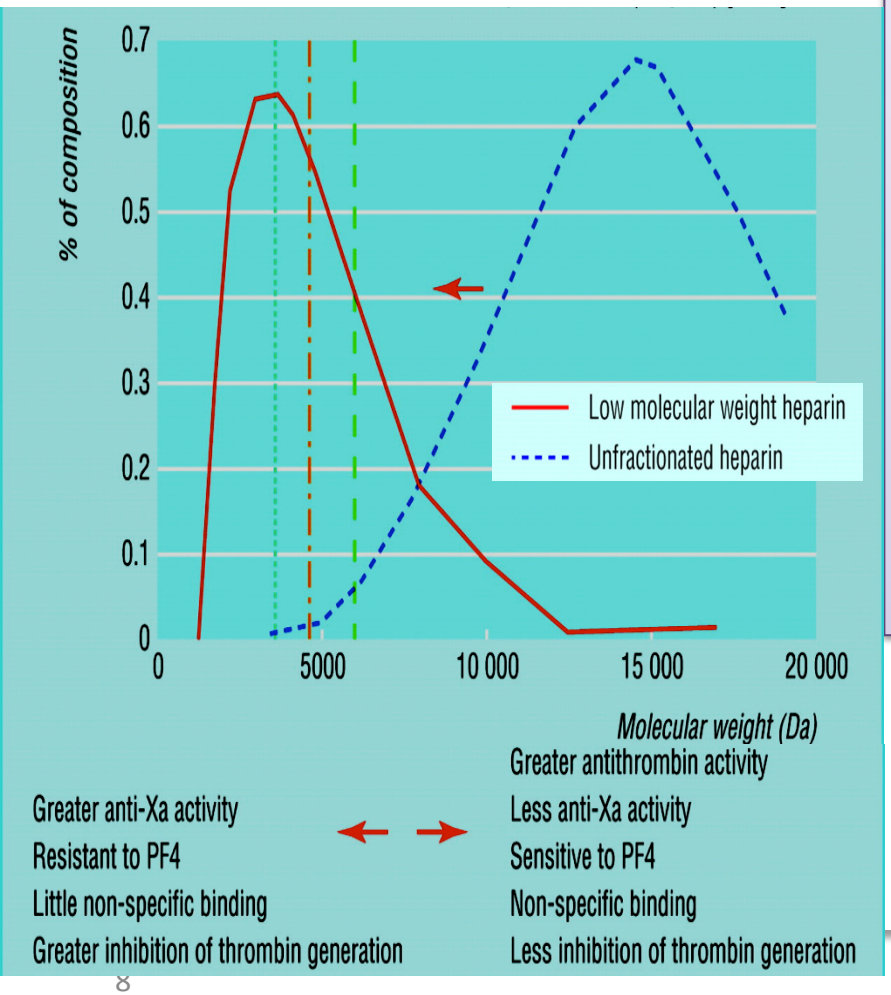
(After heparin is administered to a patient, an immune complex can form between heparin and a specific blood factor (platelet factor 4, or "**PF4**") that is released by platelets. The antibody (IgG) views this "heparin-PF4" complex as a foreign substance. Therefore, an antibody is formed against the heparin-PF4 complex. The antibody binds to this complex and the platelets are destroyed)

LMWH BENIFITS

Low molecular weight heparin

- **Predictability of anticoagulant response** ; . 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(not) sensitive to PF4 (platelet factor 4)
- ↓Incidence of bleeding tendency; ↓ effect AT III & ↓ platelet interactions
- Much better tolerability; (patient take drug without any problems)
  - given sub. cut.
  - ↓ frequency of administration due to longer duration of action
  - ↓ need for regular monitoring
  - Outside hospital settings

Ideal for old patient who can't go to the hospital ex:elderly



LMWH	UFH
Greater anti-Xa activity.	Less anti-Xa activity .
Resistent to PF4.	Sensitive to PF4.
Little non specific binding.	Non specific binding.
Greater inhibition of thrombin generation .	Less inhibition of thrombin generation

Vit. K antagonists

Activation of Precursors factors II, VII, IX & X require carboxylation of their glutamic acid residues to g-carboxyglutamate allowing factors to bind to phospholipid surfaces. This is provided by Vit. K as it changes from its oxidized to its reduced form.

The reduced Vit K has to recycle back to oxidized form by Vit K epoxide reductase. This enzyme is blocked by VKAs → losing the coagulation factors the ability to function.

Wide variation in drug response → need continuous monitoring (PT) & dose adjustment .

Has narrow therapeutic does; high plasma bind protein & action depends on very small fraction of free drug. So any change in that level can be dangerous .

Slow onset of action, so not in given in emergency conditions

Has latency in its action.

Common genetic polymorphisms in CYT P450 isoforms that metabolizes warfarin → adds to its non predictable response → toxicities or under use.

Numerous food- & drug-drug interactions → toxicities or under use.

Contraindicated in pregnancy (liable to develop deep venous thrombosis) → give heparin or LMWH instead they are safe in pregnancy .

Factors that increases response of VKAs	Factors that decreases response of VKAs
1) Vitamin K deficiency; a- **Inadequate diet.** b- **Inadequate absorption**; diseases of small intestine, diseases ↓ biliary secretion of bile salts coz vit .k fat soluble ! 2) impaired synthesis of clotting factors; a. In **hepatocellular disorders**; (hepatitis; viral, autoimmune, drug- induced, chronic alcoholism) b. **In hepatic congestion**; in congestive HF) 3) Increased catabolism of clotting factors; In **hypermetabolic states**; as in fever, thyrotoxicosis	1) Decreased plasma protein binding; ↑ **elimination of free drug & shortening of its t1/2. as pts with nephrotic syndrome (proteinuria)** 2) Decreased catabolism of clotting factors; **Hypothyroidism** 3) Hereditary resistance to oral anticoagulants

Drugs modulating response to VKAs (↑INR) (Bleeding and toxicity)	Drugs modulating response to VKAs (↓INR) (lack of effect and efficacy)
1) Inhibition of Vit. K synthesis by intestinal flora; **oral antibiotics .**	1) Inhibition of drug absorption from GIT; **cholystyramine, colestipol.**
2) Inhibition of Vit K absorption; liquid **paraffin.**	***2) Increase in synthesis of clotting factors; Vit K, oral contraceptives .***
3) Decrease in drug metabolism by microsomal **enzyme inhibitors; chloramphenicol, & cimetidine.**	3) Increase in drug metabolism by microsomal **enzyme inducers; carbamazepine, rifampicin.**
4) Displacment of the drug from protein binding sites; **phenylbutazone & salicylates.**	
5) Co-administration of drugs that increase bleeding tendency by;**decrease clotting** inhibiting platelet function; **NSAIDs.** inhibiting coagulation factors; **heparin.**	↑vit K>> ↓Warfrin ↓vit K>>↑warfrin

INR=international normalized ratio The INR is figured out using the results of the prothrombin time (PT) test, which measures the time it takes for your blood to clot. The INR is an international standard for the PT.

Summary

*LMWH : more effective on **F.Xa**
*Direct Thrombin Inhibitors: more effective **on F.IIa**
*Factor Xa Inhibitors: more effective **on F.Xa**
UFH & LMWH have a re-thrombotic action
*Clotting is **rapid and variable** & accessed by **aPT "PARENTAL" . More than 2.5 bleeding** .
*Clotting is **slow and variable** & accessed by **aPTT "ORAL"**
*Heparin >> **No predictable \ hospital setting**
*LMWH >> **predictable\ Home "S.C"**
pregnancy ➔ **give heparin or LMWH instead**
Vit K, oral contraceptives decreases efficacy of VKAs.
(UFH) causes Heparin Induced Thrombocytopenia (HIT) within 7 -10 days (immune – mediated disorder)
Bile acid sequestered (no lipid t o absorb vit .k).
⬆INR lead to Bleeding and toxicity
⬇INR lead to the lack of effect and efficacy

Cases

1) An old, peptic ulcer patient, sustained on cimetidine, has been bed ridden since a month following a major orthopedic surgery for pelvic fracture. The last week he began to complain of pain, tenderness, warmth & swelling of his left leg. He was diagnosed as deep vein thrombosis. His treating physician put him first on heparin that was replaced after three days by VKAs. Today he began to show bleeding of gums.
2) What is the expected explanation of his finding?

*Warfarin toxicity because of the enzyme inhibitor cimitidine.

Will the treating physician 1st of all, consider giving an antidote to stop bleeding (if so then state) or will he probably ask for lab investigation (if so then state)?

show bleeding of gums >> not emergency situation,so we have time to do lab investigations

Once lab findings are there, is the physician expected first to withdraw or to adjust the existing therapy?

Give him other H2 blockers, other than cimitidine

Cases

2) A young rheumatic artheritic patient has underwent valve replacement and is sustained on warfarin therapy for the last three years. When she married, last summer, she did not want to get pregnant, so she has taken since then, oral contraceptive pills.
Her regular lab monitoring today showed a decrease in INR this time.
What is the expected explanation of her lab result?
*Contraceptives indusce the coagulation factors >> tendency of thrombus

What will the treating physician consider doing?
-Giving heparin on top
-Adjusting warfarin dose
- Stopping the OC
- Stopping warfarin
Increase the dose of warfarin because still there is no thrombus formation

Cases

3) **A 53 years old patient had an aortic valve replacement since 5 years and he is sustained on warfarin. A week ago, he developed low grade fever, diarrhea and was diagnosed as having typhoid. He was given rehydration fluid and a course of chloramphenicol.**

Today he is complaining from haematuria.

Which one of the following best explains the haematuria?

- Inhibition of Vit K synthesis by chloramphenicol
- Displacement of warfarin from protein binding site by rehydration
- Decrease in warfarin metabolism induced by chloramphenicol
- Inhibition of Vit K absorption caused by the diarrhea

-Which is the right decision to do in such a case?

Give a urinary antiseptic for fear of infection

- Stop administering the regular intake of warfarin
- Adjust the dose of warfarin after monitoring the situation.
- Stop the course of chloramphenicol intended for typhoid therapy

chloramphenicol should be stopped >> Hematuria emergency

Questions

4. Patient is prescribed for anticoagulant , suddenly , he developed a tenderness, warmth & swelling of his left leg.

Which drug is most probably the one he used and what is the appropriate antidote?

A.Heparin \ Protamine Sulphate
B.LMWH \ Vit. K_1
C.Heparin \ Vit. K_1

5. Which drug is contraindicated for pregnant lady with Venous thrombosis?

A.Warfarin
B.Heparin
C.LMWH

6. Carbamazepine is giving to a patient who is taking VKI, what is the predictable result of this combination ?

A. Toxicity that leads to bleeding
B. Decrease the efficacy
C. Increase the INR

4 >> A
5 >> A
6 >> B

Questions

7. **Myocardial onfarction patient is given heparin then after 2 days rethrombosis occurred,Which drug can properly monitor his situation?**
   - A. Low molecular weight heparin
   - B. Direct thrombin inhibitors
   - C. Factor X inhibitor

8. **Pregnant lady has deep vein thrombosis , she has to take anticoagulant.. Which drug is safe to her?**
   - A. Warfarin
   - B. Heparin/LMWH
   - C. NSAIDS

9. **80 years patient has Myocardial infarction, he cant go to the hospital .. Which drug is more effective and suitable for his siutation ?**
   - A. Heparin
   - B. Warfarin
   - C. LMWH

7/B
8/B
9/c

PHARMACOLOGY

TEAM 432

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