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Pharmacology
Team 437

MED437
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Anti-coagulant drugs

Objectives:

- Introduction about 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.

★ نظراً لوجود اختلاف بين سلايدات البنات والأولاد ، تم الأعتماد على سلايدات البنات و اضفنا الكلام الموجود بسلايدات العيال باللون الأزرق.

★ بروف يلدز قالت انو سلايدز الأولاد معقدة ، و الأشياء المعقدة ما بشرحهاش ، فلذلك اعتمدنا على سلايدات البنات .

★ المشترك بين سلايدات البنات والأولاد هو اللي بيجي بالأختبار.

Editing File

Color index: Important Note Extra Only Male's slides

Mind Map

1- Parenteral Anticoagulant

Thrombin inhibitors

Indirect

Heparin (**unfractionated heparin**)
low molecular weight heparin:
★ heparin fragments → **enoxaparin,dalteparin**
★ synthetic pentasaccharide → **fondaparinux**

Direct

★ **Hirudin**
★ **Leppirudin**

2- Oral anticoagulant

Vit K Antagonist

Warfarin

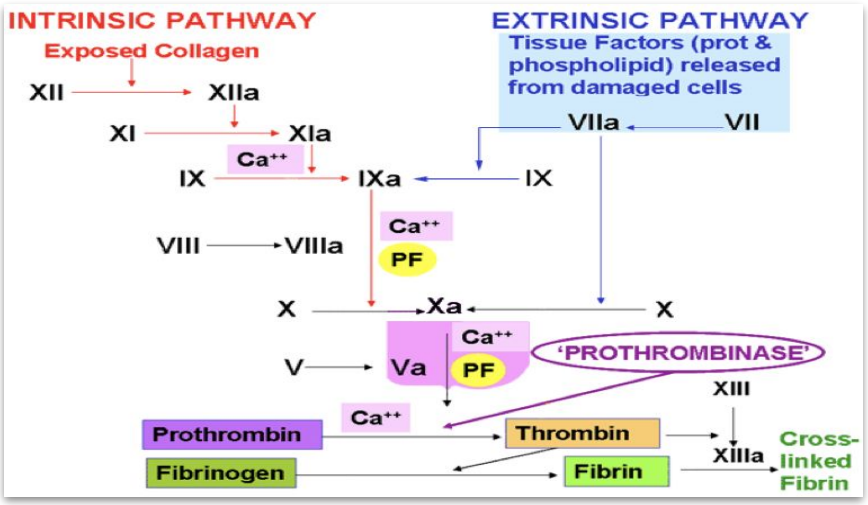
Drugs anti coagulation

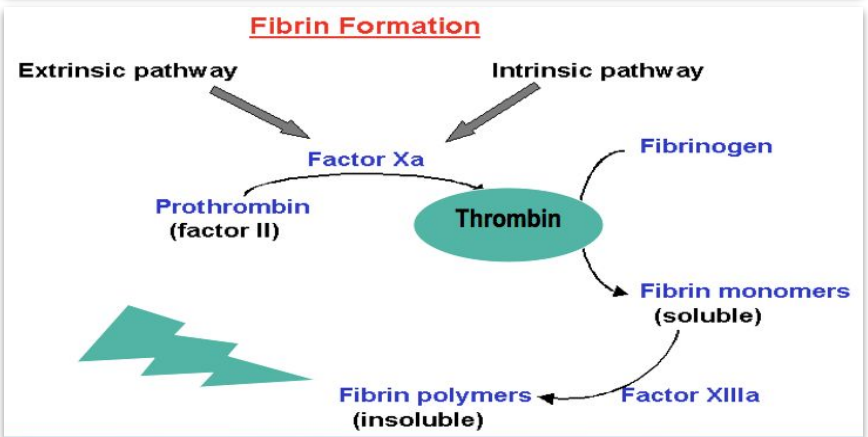
- ★ **Anticoagulants:** prevent thrombus formation and extension by inhibiting clotting factors e.g heparin, low molecular weight heparin (parenteral), coumarins/Warfarin (oral) (they inhibit the chemical process of formation of the fibrin polymer).
- ★ **Antiplatelet drugs:** reduce risk of clot formation by inhibiting platelet functions (molecules that do not allow platelets to aggregate,especially in the arteries,) e.g aspirin and ticlopidine given to high risk individuals.
- ★ **Fibrinolytic agents:** dissolve thrombi already formed (molecules that disintegrate a pre-formed clot)e.g. streptokinase (used in acute thromboembolic diseases)

Coagulation Pathways

بروف يلدز قالت ما راح نسألكم عليها

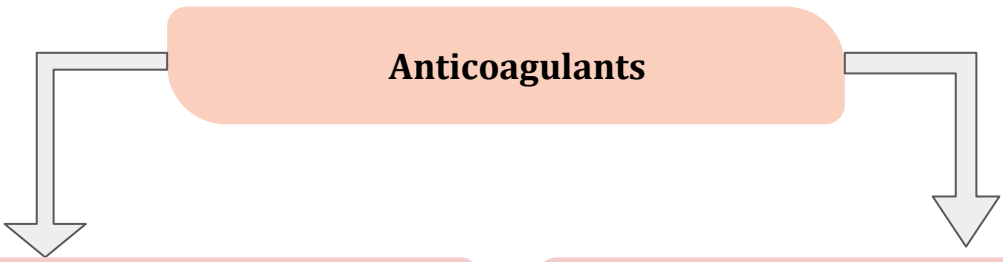
- ★ Two major pathways:
  - Intrinsic pathway
  - Extrinsic pathway
- ★ Both converge to a common pathway.
- ★ 13 soluble factors are involved in clotting which normally circulate in an inactive state and must be activated to form a fibrin clot.
- ★ All clotting factors are within the blood (tissue factor=thromboplastin)
- ★ Initiating factor is outside the blood.





Endogenous inhibitors of coagulation

- ★ Anti-thrombin III : It's a plasma protein that acts by inhibiting the activated thrombin (factor IIa) and inhibits factor Xa and other coagulation factors (VIIa, IXa, XIa and XIIa), it is the site of action of heparin.
- ★ Prostacyclin (prostaglandin I2): It is synthesized by endothelial cells and inhibits platelet aggregation.
- ★ Protein C and protein S these are vitamin K dependent proteins that slow the coagulation cascade by inactivating factor Va and VIIIa. vit k antagonists work on them



Parenteral Anticoagulant

Act as thrombin inhibitors either in: A Direct way or an indirect way
Indirect: On antithrombin lll
Direct: on thrombin

Oral Anticoagulant

Act as Vitamin K antagonist (e.g. Warfarin)

We start with parenteral and then continue on oral (because they take time to work)

Anticoagulants indications

These indications may come in scenarios

- ★ In myocardial infarction (MI) due to stagnation of blood → risk of thrombosis
- ★ Deep venous thrombosis (DVT)
- ★ Peripheral arterial emboli, pulmonary embolism(PE) and many other conditions
- ★ Also used in blood transfusions and dialysis procedures..

Parenteral Anticoagulants: Indirect Thrombin Inhibitors

Drug	Heparin (Unfractionated Heparin "UFH")
Origin	• Normally occurs as macromolecule in mast cells with histamine (its physiological role is unknown) high molecular heparin • Commercial preparations are extracted from beef lung or pig intestine **(can cause hypersensitivity reaction)**
Function	• Heparin stops the expansion of a thrombus and prevents the formation of new thrombi but it does not dissolve an existing thrombus
P.K	• Heparin is an **injectable rapidly acting anticoagulant** • Active in vitro and in vivo • Low–molecular–weight forms (LMWHs), 1/3 the size of UFH are used as well and have many advantages over UFH • Heparin is not absorbed from the GIT • It should be administered by IV or SC injection. Not injected IM as it causes haematomas at injection site • Once in the bloodstream, UFH binds to plasma proteins, endothelial cells and macrophages (low bioavailability) • Heparin does not cross the placenta; therefore it is the drug of choice as anticoagulant during pregnancy • Close monitoring of the activated partial thromboplastin time (aPTT) is necessary in patients receiving UFH
M.O.A	• Indirect Thrombin Inhibitor • It acts indirectly by increasing the activity of the endogenous anticoagulant **"antithrombin III"**(1000 folds) which inhibits **activated clotting factors** mainly thrombin ***(factor IIa)*** **"essential for clot formation"** and other serine proteases (clotting factors) e.g VIIa, IXa and particularly **Xa**. • When Heparin binds to antithrombin III, it causes conformational changes that accelerates its rate of action 1000 fold In the absence of heparin this inactivation is slow heparin acting is a cofactor accelerate the reaction by 1000-fold. • Heparin binds to both antithrombin III and thrombin to form a ternary complex • Heparin dissociates leaving the thrombin bound to its inhibitor • Once dissociated, Heparin is free to bind to another antithrombin molecule and subsequently inhibits more thrombin Therefore one molecule of heparin can bind multiple antithrombin III-Thrombin complexes

Indirect Thrombin Inhibitors (cont'd)

Uses	• Due to its rapid onset of action, it is used to **initiate immediate anticoagulation** in thromboembolic disease (PE, DVT, MI) mainly as induction for oral vitamin K antagonists (VKAs) • **Prevention of postoperative DVT (in patient undergoing hip replacement)** • Prevention of coagulation during renal dialysis or cardiac surgery(indicated in long surgical operations)
Disadvantages	• The inconvenience of administration by injection and requires multiples doses due to short half life (2 hours) • No predictable anticoagulant effects; inter-patient & intra-patient variability in response to a given dosage - in hospital setting, The need for regular monitoring (aPTT) • Re-thrombosis(major limitation of heparin therapy) → activates platelets as it does not neutralize fibrin-bound II a. • In emergency we use three drugs: 1-antiplatelet 2-anticoagulant 3-fibrinolytic • Low bioavailability (Which will cause decrease in response) → binds to plasma protein, endothelium & macrophages. • UFH carries a risk of heparin-induced thrombocytopenia, a fall in the platelet count and increased risk of thrombosis due to binding to platelets (This is a characteristic of heparin)
Heparin-Induced Thrombocyto-penia (HIT)	• Generally, if the number of platelets is too low, excessive bleeding can occur • If the number of platelets is too high, blood clots can form thrombosis • However, There are disorders that reduce the number of platelets, such as heparin-induced thrombocytopenia (HIT) that typically cause thrombosis, or clots, instead of bleeding (life threatening condition) • HIT: In 4% pts. on heparin, latency 5-10 dys. after 1st exposure or 2-3 days. after re-exposures → Venous → Arterial thombosis • Heparin discontinuation will lead to no packed platelets → More thrombosis, No warfarin → ppt.venous gangrene, Give → DTIs. Why? Because they work on 1-thrombin which is bound fibrin (thrombus) 2-free thrombin

Indirect Thrombin Inhibitors (cont'd)

ADRs	• The major adverse effect of heparin is bleeding • Allergic reactions (chills, fever, urticaria) as heparin is of animal origin and should be used cautiously in patients with allergy • Long-term heparin therapy is associated with osteoporosis (heparin binds to osteoblasts) • **Heparin-induced thrombocytopenia (HIT)**
C.I.	• Bleeding disorders, hemophilia • Patients with hypersensitivity to the drug • Recent surgery of the brain, eye or spinal cord, threatened abortion
Reversal of Heparin Action	1. Discontinuation of the drug First thing you MUST do 2. Heparin is strongly acidic and is neutralized by i.v. protamine sulfate (a strongly basic protein) • It combines with heparin to form a stable complex devoid of anticoagulant activity

Indirect Thrombin Inhibitors

Low-Molecular-Weight Heparins (LMWHs)

	Heparin fragments (enoxaparin, dalteparin)	Synthetic pentasaccharide (fondaparinux)
M.O.A	LMWHs increase the action of antithrombin III on factor Xa but not its action on thrombin, because the molecules are too small to bind to both enzyme and inhibitor.	
Uses	increasingly in place of unfractionated heparin.	
Advantages	• LMWHs are derived from the chemical or enzymatic degradation of UFH into fragments approximately one-third the size of heparin. • The theoretical pharmacologic advantages of LMWH over UFH arise from the preferential binding ratio to factor Xa over thrombin. • Have equal efficacy, without frequent laboratory monitoring (suitable for outpatient therapy) • Have a more predictable anticoagulant response i.e. little inter-patient and intra-patient variability in response to a given dosage. • better bioavailability as it hardly binds to plasma proteins, endothelium & macrophages • Much better tolerability ,given subcutaneously → Reduced frequency of administration due to longer duration of action(once or twice daily) due to longer t ½ so lessens need for regular monitoring outside hospital settings • Binding to platelets and osteoblasts is reduced with LMWH compared with UFH • Less plasma protein binding. • Less platelet activation and lower risk of re-thrombosis and thrombocytopenia • Decreased incidence of thrombocytopenia; as it seldom sensitive to PF4. • Decreased incidence of bleeding tendency; decrease effect AT III & decrease platelet interactions.	

Synthetic Heparin Derivatives (fondaparinux)

M.O.A	a synthetic compound that inhibits factor Xa by antithrombin but does not inhibit thrombin
Advantages	• can be given once a day at a fixed dose without coagulation monitoring • Less likely than UFH or LMWHs to trigger HIT

Differences between UFH and LMW Heparins

Drug characteristics	Heparin (UFH)	LMWH
IV ½ life	2 hours	4 hours
Bioavailability after SC injection	20%	90%
Anticoagulant response	variable	Predictable
Major adverse effect	Frequent bleeding HIT, osteoporosis	Less frequent bleeding Less
Specific antagonist	Protamine sulphate Complete antagonism of heparin	-Incomplete- Incomplete antagonism of LMWH
Setting for therapy	Hospital	Hospital and OPC (outpatient clinic)
Laboratory monitoring	Needed **aPTT**	Not needed

Direct Thrombin Inhibitors (DTIs)

Drug	**Hirudin** First to be developed was isolated from the saliva of the leech علقة	**Lepirudin** polypeptide that binds directly to the active site of thrombin
M.O.A	Exert their effect by direct binding to thrombin.	
Advantages	★ This direct effect is rapid & potent. ★ Not associated with thrombocytopenia. ★ Recombinant hirudin "Lepirudin" is used as IV anticoagulant in patients with HIT (Heparin-induced thrombocytopenia) ★ Lepirudin, like heparin, it must be administered parenterally and is monitored by the aPTT.	

Oral Anticoagulants
"Vitamin K antagonists"

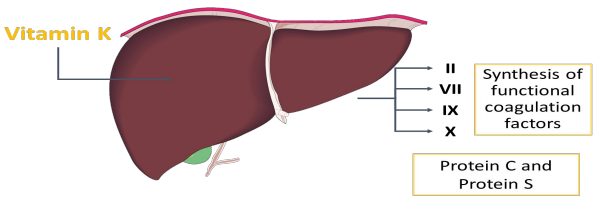
Vitamin K (Fat soluble vitamins)

★ Source of vitamin:
green vegetables Synthesized by normal flora.

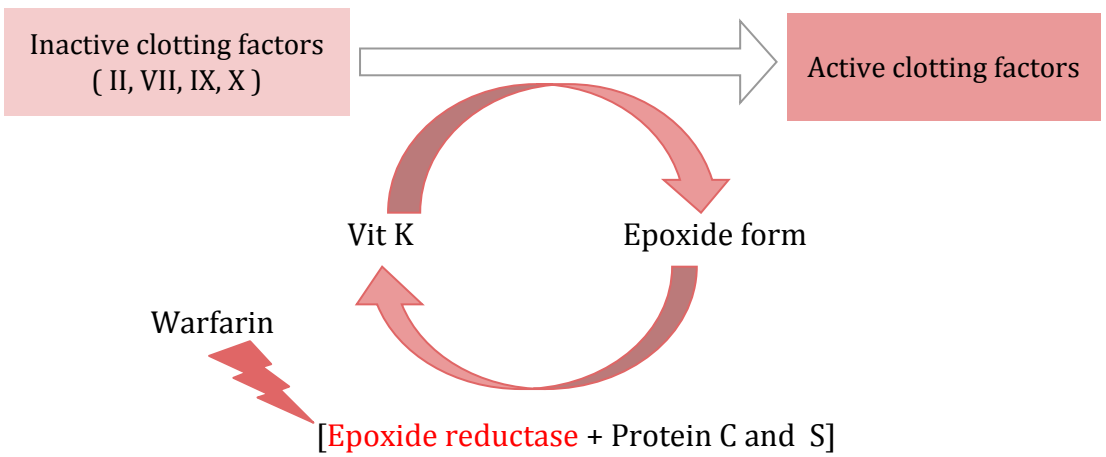
★ Required for synthesis(Vitamin K Vitamin K-Dependent Clotting Factors):

★ Factors II, VII, IX ,X (Synthesis of functional coagulation factors) & Protein C and S (endogenous anticoagulants)

★ Causes of deficiency:
- ➔ Malnutrition
- ➔ Malabsorption
- ➔ Antibiotic therapy



- **Warfarin: Mechanism of action**



Vitamin K (Fat soluble vitamins)Antagonist

Drug	Coumarin (Warfarin)
M.O.A	• It inhibits the synthesis of biologically active forms of vitamin K-dependent clotting factors II, VII, IX and X as well as anticoagulant proteins C & S. • 3-4 days until effect is seen. Therefore immediate anticoagulation is provided by Heparin (can't give warfarin in acute situations) • Does not have any effect on already-synthesized coagulation factors; therefore, the therapeutic effects are not seen until these factors are depleted.(this is also why when warfarin in stopped its effects continue for 3-4 days)

Vitamin K (Fat soluble vitamins) Antagonist (cont'd)

P.K	- Act only in vivo - Bioavailability 100% -98% bound to plasma proteins (albumin) (therefore its liable to drug-drug interactions) -Monitoring anticoagulant effect of warfarin by measuring PT, which is expressed as an International Normalized Ratio (INR) -Their effect takes several days (3-4) to develop because of the time taken for degradation for circulating functional coagulate factors -Therefore the onset of action starts when these factors have been eliminated -Warfarin has a slow offset of action due to the time required for synthesis of new functional coagulation factors.
Disadvantages	• Variable, unpredictable effect necessitating regular INR monitoring and dose adjustment. • Narrow therapeutic window leading to increased risk of severe bleeding. • Slow onset and offset of action. • Numerous interactions with foods containing vitamin K and drugs.
Drug interactions with oral anticoagulants **Extremely important**	★ **Increase activity of Warfarin: Lead to bleeding** 1.Inhibition of Vit. K synthesis by intestinal flora; oral antibiotics 2. Inhibition of Vit K absorption; liquid paraffin 3. Decrease in drug metabolism by microsomal enzyme inhibitors, chloramphenicol & cimetidine 4. Displacement of the drug from protein binding sites;phenylbutazone & salicylates. (eg. Asprin) 5. Co-administration of drugs that increase bleeding tendency by; inhibiting platelet function; NSAIDs, heparin. (NSAIDS both displace drug from plasma proteins and have an antiplatelet effect) * "Example question: Which of the following will increase the activity of warfarin?" ★ **Decrease activity of Warfarin:** 1.Increase in drug metabolism by microsomal enzyme inducers; Carbamazepine; barbiturates, rifampicin 2.Inhibition of drug absorption from GIT; cholystyramine, colestipol 3.Increase in synthesis of clotting factors; Vitamin K ,oral contraceptives
C.I.	• **pregnancy** as it can cross the placental barrier and cause **abortion**, **hemorrhagic disorder** in the fetus and **birth defects** (Teratogenicity).
Reversal of action (antidote)	If the patient develop Bleeding due to Warfarin: • Stop the drug • IV injection of vitamin K • Fresh frozen blood or plasma

Cases from Dr slides

Case 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.

Cimetidine inhibit the anticoagulant , so we use any other drug for the ulcer like Omeprazole

Case 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?
Warfarin isn't working.
What will the treating physician consider doing?
A-Giving heparin on top
B-Adjusting warfarin dose
C- Stopping the OC
D- Stopping warfarin
Answer C

بروف يلدز قالت أن السميري مراجعة
للكلام اللي موجود بالسلايدز، يعني قراءة

Summary from Dr. slides

Table VII-1-1. Properties of Heparin and Warfarin (Coumarins)

Feature	Heparin(s)	Warfarin (Coumarins)
Chemical Nature	Large polysaccharide, water-soluble	Small molecule, lipid-soluble derivatives of vitamin K
Kinetics	Given parenterally (IV, /SC), hepatic and reticuloendothelial elimination, half-life = 2 h, no placental access	Given orally, 98% protein bound, PO, liver metabolism, half-life = 30+ h, placental access
Mechanism	↑ Activity of antithrombin III, resulting in the inactivation of factors IIa and Xa. Actions *in vivo* and *in vitro*.	↓ Hepatic synthesis of vitamin K–dependent factors II, VII, IX, X—coumarins prevent γ–carboxylation; no effect on factors already present. In *vivo* effects only.
Monitoring	Partial thromboplastin time (PTT)	Prothrombin time (PT); INR

Table VII-1-1. Properties of Heparin and Warfarin (Coumarins) (continued)

Antagonist	Protamine sulfate—chemical antagonism, fast onset	Vitamin K–↑ cofactor synthesis, slow onset; fresh frozen plasma—fast
Uses	Rapid anticoagulation (intensive) for thromboses, emboli, unstable angina, disseminated intravascular coagulation (DIC), open-heart surgery, etc.	Longer-term anticoagulation (controlled) for thromboses, emboli, post-MI, heart valve damage, atrial arrhythmias, etc.
Toxicity	Bleeding, osteoporosis, heparin-induced thrombocytopenia (HIT), hypersensitivity	Bleeding, skin necrosis (if low protein C), drug interactions, teratogenic (bone dysmorphogenesis)

Summary

Indirect thrombin inhibitor	
Drug	**Unfractionated Heparin**

- **<u>stops the expansion</u>** of a thrombus by increasing the activity of **"antithrombin III"**(1000 folds) which inhibits **activated clotting factors** mainly thrombin ***(factor IIa)*** and particularly **Xa**. (which means at M.O.A is indirect)
- **<u>prevents the formation</u>** of new thrombi
- **<u>DOES NOT dissolve</u>** an existing thrombus
- Drug of choice as anticoagulant during pregnancy
- **initiate immediate anticoagulation in thromboembolic disease**
- **Prevention of postoperative DVT**
- Need close monitoring of the activated partial thromboplastin time (**aPTT**)
- Can cause heparin induces thrombocytopenia (**HIT**)
- The **major adverse effect** of heparin is bleeding Allergic reactions (chills, fever, urticaria)
- Discontinuation of the drug Is the first step of **reversal of heparin action**
- **Antidote**: protamine sulfate

Low-Molecular-Weight Heparins (LMWH)		
Drug	**Heparin fragments (e.g. enoxaparin, dalteparin)**	**Synthetic pentasaccharide (fondaparinux)**

•LMWHs increase the action of antithrombin III on factor Xa but not its action on thrombin
•Have equal efficacy, without frequent laboratory monitoring **(suitable for outpatient therapy)**

Direct thrombin inhibitor		
Drug	**Hirudin**	**Lepirudin**

Vitamin K Antagonist	
Drug	**Coumarins: Warfarin**

- It inhibits the synthesis of biologically active forms of vitamin K-dependent clotting factors II, VII, IX and X as well as anticoagulant proteins C & S
- **Narrow therapeutic window**
- **Monitoring anticoagulant effect of warfarin by measuring International Normalized Ratio (INR)**
- **Increase activity of Warfarin:**

➔ oral antibiotics -liquid paraffin -chloramphenicol & cimetidine-phenylbutazone & salicylates -NSAIDs, heparin

➔ **Decrease activity of Warfarin:**

➔ Carbamazepine; barbiturates, rifampicin - cholystyramine, colestipol - Vitamin K ,oral contraceptives

- Contraindicated during pregnancy
- Antidote → vitamin k , fresh frozen blood

MCQs

1- which of the following is the site of action of Heparin as an anticoagulant?
A- Prostacyclin I2
B- Protein C
C- Antithrombin III
D- Fribrinogen.

2- a pregnant woman in her first trimester was on a 16 hour long flight and subsequently developed deep vein thrombosis. Which of the following drugs would be best used in her case?
A- Lepirudin.
B- Streptokinase.
C- Heparin.
D- Warfarin

3-All of the following are disadvantages of Unfractionated Heparin except :
A- Patients need close monitoring of the aPTT.
B- slow onset of action.
C- risk of thrombocytopenia.
D- inconvenience of constant administration by injection.

4- which one of the following is an antidote of heparin ?
A- N-acetylcysteine.
B- protamine sulfate.
C- octreotide.
D- L-carnitine.

5- all of the following are indirect thrombin inhibitors except :
A- enoxaparin.
B-dalteparin.
C- fondaparinux.
D- lepirudin.

6- which of the following drugs is least likely to trigger heparin induced thrombocytopenia?
A- unfractionated heparin .
B- enoxaparin
C- dalteparin
D- Fondaparinux.

MCQs:

7- a patient with a myocardial infarction was admitted to the hospital and put immediately on IV Heparin. Upon monitoring , he developed thrombocytopenia , but despite that suffered from frequent thrombosis. Which of the following anticoagulants is best used to manage his case?
A- Lepirudin.
B- Dalteparin.
C-Enoxaparin.
D- Warfarin.

8-which of the following increases the effect of warfarin?
A- colestipol.
B- barbiturates.
C- Cholestyramine.
D- Chloramphenicol.

Answers:
1- C
2- C
3- B
4- B
5- D
6- D
7- A
8-D

SAQ:

Q1:A patient undergoing a hip replacement surgery is given warfarin to prevent the risk of developing deep vein thrombosis. What is the mechanism of action of warfarin ?

It inhibits the synthesis of biologically active forms of vitamin K-dependent clotting factors II, VII, IX and X as well as anticoagulant proteins C & S.

Q2: List two methods by which we can enhance the effect of warfarin , and two methods that decrease the effect of it.

Drugs that enhance its effect include :

1-salicylates (by displacing the drug from protein binding site)
2-Chloramphenicol and Cimetidine (Microsomal enzyme inhibitors).

Drugs that decrease its effect :

1- Cholestyramine and Colestipol (inhibit drug absorption from GIT)
2- Carbamazepine , barbiturates , rifampicin (Microsomal enzyme inducers)

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References:

✓ Doctors' slides and notes

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