MED438

pharmacology
Team 438

Reviewed by Razan AlRabah & Ibrahim AlDakhil

Anticoagulant Drugs

Objectives:

By the end of the lecture , you should know:

- Introduction about coagulation cascade
- Classification of 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 index:

Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

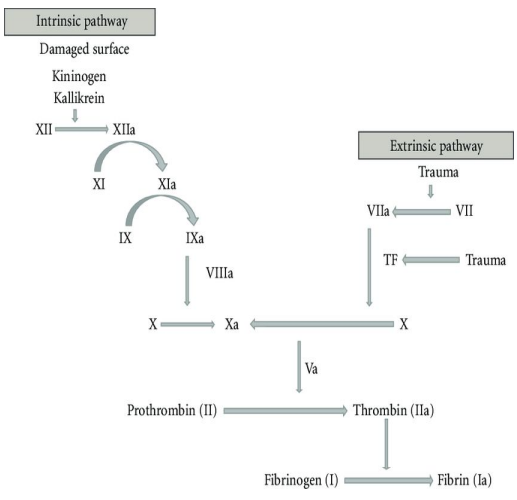
Editing File

Drugs Anti Coagulation

- **Anticoagulants: prevent thrombus formation and extension** by **inhibiting clotting factors** e.g heparin, low molecular weight heparin, coumarins/Warfarin
- **Antiplatelet Drugs:** reduce risk of clot formation by **inhibiting platelet functions** e.g aspirin and ticlopidine
- **Fibrinolytic agents:** dissolve thrombi **already formed** e.g. streptokinase

Coagulation Pathways

1. Two Major pathways: 1. Intrinsic pathway
   2. Extrinsic pathway
2. Intrinsic pathway: All clotting factors are within the blood (tissue factor=thromboplastin)
3. Extrinsic pathway: Initiating factor is outside the blood.



4. Both converge to common pathway
5. 13 soluble factors are involved in clotting which normally circulate in an inactive state and must be activated to form a fibrin clot.
6. **Endogenous Inhibitors of Coagulation:**

Antithrombin III: Antithrombin III, is a plasma protein that inhibits activated thrombin (factor IIa) and Xa, **it is the site of action of heparin.**
It inactivates thrombin and other coagulation factors (IXa, Xa, XIa and XIIa) by forming complex with these factors. Heparin like molecules enhances these interactions.

Prostacyclin (prostaglandin I2): It is synthesized by endothelial cells and inhibits platelet aggregation. [1]

Protein C and protein S: these are vitamin K dependent proteins that slow the coagulation cascade by inactivating factor Va and VIIIa.

1) They have an antiplatelet effect (not an anticoagulant).

Parenteral[1]

Act as **thrombin inhibitors** either in: A **direct way**[2] or an **indirect way**[3]

Anticoagulants

Oral

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

Parenteral Anticoagulants				Oral
Unfractionated heparin	Low Mol. Weight Heparin	Direct Thrombin Inhibitors	Factor Xa inhibitors	Vit. K antagonists
3000-30000	<800		Pentasaccharide	Coumarins; Warfarin > 40 potency than Dirumarol
	>Xa	IIa	Xa	
	Enoxaparin Dalteparin	Bivalirudin R Lepirudin IR Argatroban R Dabigatran R(Oral)	Fondaparinux IR Rivaroxaban R (Oral)	

Anticoagulant Indications

1. Myocardial infarction (MI)
2. Deep venous thrombosis (DVT)
3. Peripheral arterial emboli, pulmonary embolism (PE) and many other conditions
4. Blood transfusions and dialysis procedures

Parenteral Anticoagulants

1) Indirect Thrombin Inhibitors

Unfractionated heparin "UFH"

Drug	Heparin (Unfractionated heparin "UFH")
Origin	• Normally occurs as macromolecule in mast cells with histamine (its physiological role is unknown) • 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** [4] • 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 [5] ★ 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

1) Heparin and Heparin-like drugs.
2) Directly acts on thrombin molecule and deactivate it.
3) Acts on Antithrombin which will in turn act on factor 2 and 10.
4) Used in **emergencies** and followed by oral anticoagulants.
5) Thus it has an unpredictable adverse effects when taken at a high dose.

1) Indirect Thrombin Inhibitors CONT...

Drug	Heparin (Unfractionated heparin "UFH")
MOA	★ It acts indirectly by **increasing the activity** of the endogenous anticoagulant **"antithrombin III"** (1000 folds) which **inhibits activated clotting factors mainly thrombin (factor IIa),** other serine proteases (clotting factors) e.g VIIa, IXa **and particularly Xa,** The anti-coagulant effect of heparin is mediated via anti-thrombin III • In the absence of heparin this inactivation is slow, when Heparin binds to antithrombin III (heparin acting is a co-factor), it causes conformational changes that accelerates its rate of action 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
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
Dis-advantage	★ **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 discontinuation → No packed platelets → More thrombosis No warfarin→ precipitate venous gangrene, **give → Direct thrombin inhibitor** • The inconvenience of administration by injection • The need for regular monitoring (aPTT) ★ UFH carries a risk of **heparin-induced thrombocytopenia, a fall in the platelet count and increased risk of thrombosis** due to binding to platelets ○ 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. ○ It happen in 4% pts. on heparin, latency 5-10 days. after 1st exposure or 2-3 days. after re-exposures →Venous → Arterial thrombosis
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** [1] ★ **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
Reverse Heparin Action	• Discontinuation of the drug ★ Heparin is strongly acidic and is **neutralized by i.v. protamine sulfate** (a strongly basic protein) [2] ○ It combines with heparin to form a stable complex devoid of anticoagulant activity

1) Heparin causes increased bone resorption by stimulating osteoclasts and suppressing osteoblast function, leading to decreased bone mass. Other proposed mechanisms include depletion of mast cells in bone marrow and enhancement of parathyroid hormone (PTH) function, an important regulator of calcium in the body. The actions of PTH increase the release of calcium and phosphorus from bone into the blood to elevate serum levels; PTH is usually released in response to low serum calcium levels.

2) What's the treatment of bleeding caused by UFH?

1) Indirect Thrombin Inhibitors CONT...

Low-Molecular-Weight Heparins (LMWHs)

LMWHs are derived from the chemical or enzymatic degradation of UFH into fragments approximately one-third the size of heparin.

Drug	Heparin fragments (enoxaparin, dalteparin)	Synthetic pentasaccharide (fondaparinux)
MOA	• LMWHs **increase the action of antithrombin III on factor Xa (ONLY)** but not its action on thrombin, because the molecules are too small to bind to both enzyme and inhibitor.	
Uses	• Used increasingly in place of unfractionated heparin.	
Advantage	★ ↑ **Predictability** of anticoagulant response i.e. little inter-patient and intra-patient variability in response to a given dosage. **without the need for laboratory monitoring (suitable for outpatient therapy)** ★ **Good bioavailability**; as it hardly binds to plasma proteins, endothelium & macrophages. ★ **↓Incidence of thrombocytopenia;** as it seldom sensitive to PF4. • ↓Incidence of bleeding tendency; ↓ effect anti thrombin III & ↓ platelet interactions. • ↓Binding to platelets and osteoblasts • Less platelet activation and lower risk of re-thrombosis and thrombocytopenia; **Fondaparinux is less likely than UFH or LMWH to trigger HIT** • Much better tolerability; ○ given subcutaneously ○ ↓ frequency of administration due to longer duration of action ○ ↓ need for regular monitoring ○ Outside hospital settings	

Differences between UFH and LMWH Heparins

Heparin (UFH)

IV ½ life
2 hours

Bioavailability after SC injection
20%

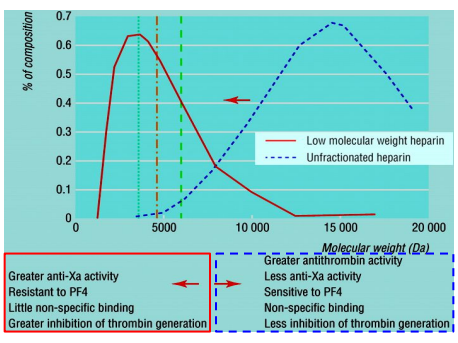
Anticoagulant response
Variable

Major adverse effect
Frequent bleeding, HIT, osteoporosis

Specific Antagonist
Protamine sulfate

Setting for Therapy
Hospital

Laboratory Monitoring
Needed aPTT



This is important! In case you were asked about the differences between LMWH and UFH

LMWH

IV ½ life
4 hours

Bioavailability after SC injection
90%

Anticoagulant response
Predictable

Major adverse effect
Less frequent bleeding

Specific Antagonist
Incomplete
Cannot be completely antagonized

Setting for Therapy
Hospital and outpatient clinic

Laboratory Monitoring
Not needed

2) Direct Thrombin Inhibitors (Females' slides)

Drug	Hirudin	Lepirudin
Info	First to be developed, was isolated from the saliva of the leech	polypeptide that binds directly to the active site of thrombin
MOA	• Exert their effect by **direct binding to thrombin.** • This direct effect is **rapid & potent.**	
Advantage	★ Are not associated with thrombocytopenia. • Recombinant hirudin "Lepirudin" is used as IV anticoagulant in patients with **HIT** (Heparin-induced thrombocytopenia)	

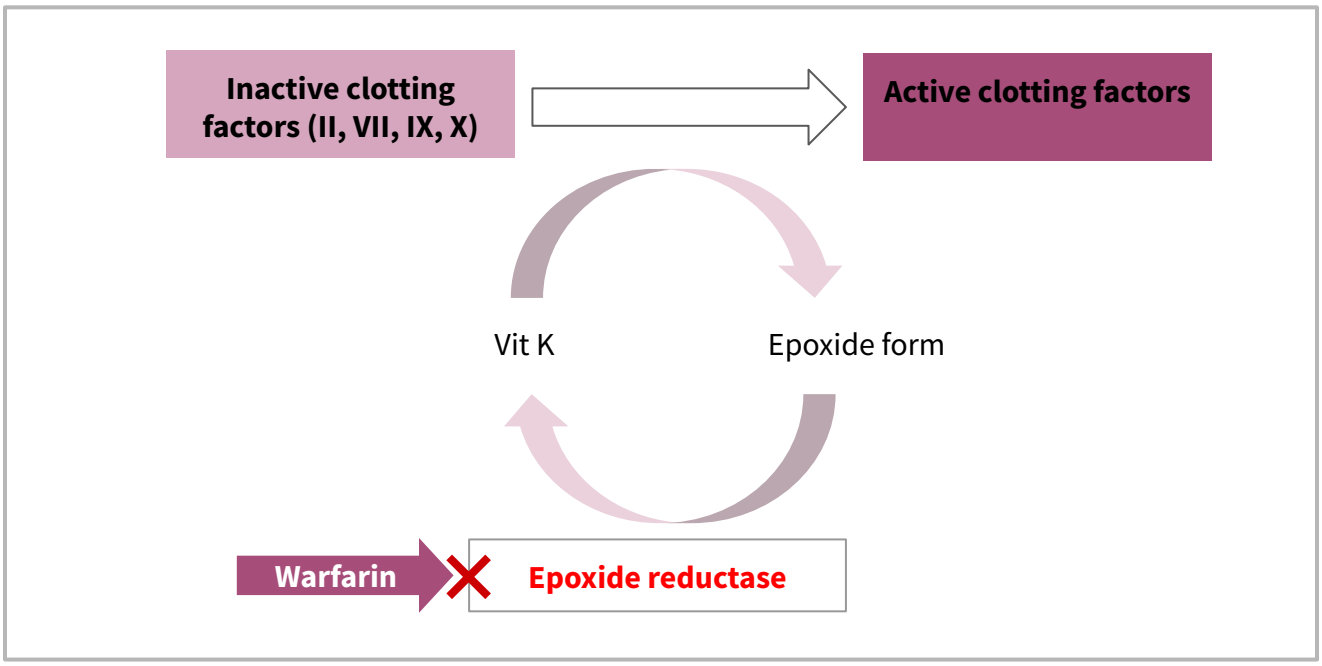
Oral Anticoagulants "Vitamin K Antagonists"

Source of vitamin:
Green vegetable synthesized by normal flora

Required for synthesis:
-Factors II, VII, IX, X
- Protein C and S
(endogenous anticoagulants)

Causes of deficiency:
-Malnutrition
-Malabsorption
-Antibiotic therapy

★ M.O.A of Warfarin



1. Precursors of factors II, VII, IX & X require **carboxylation** of their glutamic acid residues to allow them to bind to phospholipid surfaces, this is provided by Vit. K as it changes from its oxidized to its reduced form.
2. Instantaneously , the reduced Vit K has to recycle back to oxidized form by **Vit K epoxide reductase**.
3. This enzyme is blocked by Vitamin K Antagonists → losing the coagulation factors the ability to function.

Drug	Coumarin (Warfarin)
MOA	• Inhibits synthesis of Vitamin K-dependent coagulation factors II, VII, IX, & X as well as anticoagulant proteins C & S • 3-4 days until effect is seen, **Why?** ○ **Does not have an effect on already-synthesized coagulation factors**; therefore, the therapeutic effects are not seen until these factors are depleted
P.K	• Act only in **vivo** • Bioavailability 100% • 98% bound to plasma proteins (albumin)[1] • 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
Dis-advantage	★ Variable, unpredictable effect **necessitating regular INR monitoring** and dose adjustment ★ **Narrow therapeutic window**,so any change in that level can be hazardous leading to increased risk of severe bleeding ★ Slow onset and offset of action, so **not in given in emergency conditions** • Numerous food- & drug-drug interactions and Polymorphism in CYT P450 isoforms that metabolizes warfarin adds to its unpredictable response → liability to toxicities or under use.

Drug inter-actions 	• **Increase Warfarin activity**
	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**
	5. Co-administration of drugs that increase bleeding tendency by;
	  a. Inhibiting platelet function; **NSAIDs**
	  b. Inhibiting coagulation factors; **heparin**
	• **Decrease Warfarin activity**
	1. Inhibition of drug absorption from GIT; **cholystyramine, colestipol**
	2. Increase in synthesis of clotting factors; **Vit K, oral contraceptives**
	3. Increase in drug metabolism by microsomal enzyme inducers; **Carbamazepine; barbiturates, rifampicin**

C.I	• **pregnancy** as it **can cross the placental barrier** and cause abortion, hemorrhagic disorder in the fetus and birth defects → **give heparin or LMWH instead**
Reverse Heparin Action	If the patient develops bleeding due to Warfarin: • Stop the drug • IV injection of vitamin K • Fresh frozen blood [2]

1) Increased risk for drug-drug interactions.
2) Because it contain activated clotting factors.

Factors that Alter the response to VIT K Antagonists (Males' slides)

Factors increase the response

Vitamin K deficiency

Inadequate diet:
-Malnutrition
-Dieting
-Decreased GI absorption

Impaired synthesis of clotting factors

Hepatocellular disorders:
-Hepatitis; infective or chronic alcoholism

Increased catabolism of clotting factors

In hypermetabolic states; as in fever, thyrotoxicosis

Factors decrease the response

Decreased plasma protein binding

↑elimination of free drug & shortening of its t1/2
E.g patient with nephrotic syndrome (proteinuria)

Decreased catabolism of clotting factors

Hypothyroidism

Genetic

Hereditary resistance to oral anticoagulants

Comparison Between Heparin and Warfarin

Drugs	Heparin	Warfarin
Chemical nature	• Large polysaccharide, water soluble	• Small molecule, lipid soluble derivatives of vit k
MOA	• ↑ Activity of Antithrombin III, resulting in the inactivation of factor IIa and Xa. • Action in vivo and vitro	• ↓Hepatic synthesis of vit k-dependent factors II, VII, IX, X by prevent their carboxylation. • Has no effect on factors already present. • Action in vivo only
P.K	• Given parenterally (IV,SC) • Hepatic and reticuloendothelial elimination • Half life = 2 h • Does not cross placenta	• Given orally • 98% protein bound • Liver metabolism • Half life= 30+ h • Cross placenta
Monitoring	• Partial thromboplastin time (PTT)	• Prothrombin time (PT) ; International Normalized Ratio (INR)
Antagonist (Antidot)	• Protamine sulfate (chemical antagonism, fast onset)	• ↑Vit k cofactor synthesis (slow onset) • Fresh frozen plasma (fast onset)
Uses	• Rapid anticoagulation (intensive) for: • Thromboses, emboli, unstable angina disseminated intravascular coagulation (DIC), open heart surgery ...etc	• Long term anticoagulation (controlled) for: • Thromboses, emboli, post MI, heart valve damage , atrial arrhythmias ...etc
Toxicity	• Bleeding • Osteoporosis • HIT • Hypersensitivity	• Bleeding • Skin necrosis (if low protein C) • Drug interactions • Teratogenic (bone dysmorphogenesis)

Quiz

MCQ

1- Which must heparin bind to in order to exert its anticoagulant effect?

A- Thrombin B- Antithrombin III C- von Willebrand factor

2- Which is most appropriate for reversing the anticoagulant effect of heparin?

A- Aminocaproic acid B- Protamine sulfate C- Vitamin K_1

3- What factor is inhibited by Fondaparinux in conjunction with antithrombin? ?

A- Factor Xa B- Factor IIa C- Factor VI

4- What of the following drugs increases warfarin activity?

A- Barbiturate. B- Oral contraceptive C- NSAIDs

5- What test is used to monitor the effect of warfarin?

A- Prothrombin time (PT)/International normalized ratio (INR) (PT/INR) Test
B- Polymerase Chain Reaction (PCR) C- Bleeding timed (BT)Test

SAQ

1-2.A 35-years-old pregnant woman in her first trimester was on a 16 hour long flight and subsequently developed deep vein thrombosis.
Q1-Which drug would be best used in her case?
Q2-What is the M.O.A of that drug?

Q3-A male patient brought to the ER with signs of allergic reaction, when taking history his relative mentioned that he recently started taking heparin, What is the best treatment in this case?

Q4-A 80-year-old male is taking warfarin indefinitely for the prevention of deep venous thrombosis. He is a compliant patient with a stable INR and has no issues with bleeding or bruising. He is diagnosed with a urinary tract infection and is prescribed an oral antibiotic. What effect will this have on his warfarin therapy?

Q5-Mention 2 drugs that decrease activity of Warfarin.

Answers:

MCQ

Q1	B
Q2	B
Q3	A
Q4	C
Q5	A

SAQ

Q1	Heparin
Q2	Indirect Thrombin Inhibitor by increasing the activity of "antithrombin III"which inhibits mainly thrombin and Xa.
Q3	IV protamine sulfate
Q4	Increase activity of Warfarin by inhibiting synthesis of vitamin K
Q5	Rifampicin - oral contraceptive (any drug from slide 7)

Share with us your ideas !

Good Luck , Future Doctors!

Team Leaders:

May Babaeer

Zyad Aldosari

This Amazing Work Was Done By:

Deana Awartani

Nouf AlShammari

Noura AlMazrou

Shahad AlSahil