Revised & Approved

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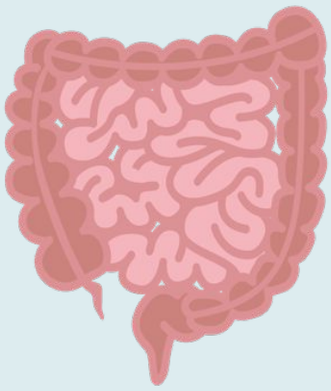
Pharmacology 439

MED439



Gastrointestinal Block

Pharmacology Team 439

Helpful video

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Anti-Coagulant Drugs

We highly recommend studying physiology of coagulation before this lecture

Objectives:

1- Introduction about coagulation cascade

2- Classification of drugs acting as anticoagulants

3- Elaborate on their mechanism of action, correlating that with methods of monitoring.

4- Contrast the limitations & benefits of injectable anticoagulants in clinical settings.

5- Emphasis on the limitations of VKAs & on variables altering or modifying their response.

6- Apply such variability in a clinical scenario

Editing file | Summary

Anticoagulants drugs

Drugs Anti Coagulation

Antiplatelet Drugs:
Molecules that do not allow platelets to aggregate and thus prevent clotting, especially in the arteries

- **aspirin**
- ticlopidine

Anticoagulants:
are molecules that prevent blood from clotting. They inhibit the chemical process of formation of the fibrin polymer (MOA).

- heparin
- low molecular weight heparin
- coumarins/ Warfarin (vitamin K antagonist)

Fibrinolytic agents:
Molecules that disintegrate a pre-formed clot

- Streptokinase (Enzyme)

Anticoagulant and Antiplatelet drugs are for prevention while fibrinolytics are for treatment. All of them can be combined in emergencies

Coagulation Pathways:

*Extra: only the pictures are found

1. *Two Major pathways: a. Intrinsic pathway
   b. Extrinsic pathway

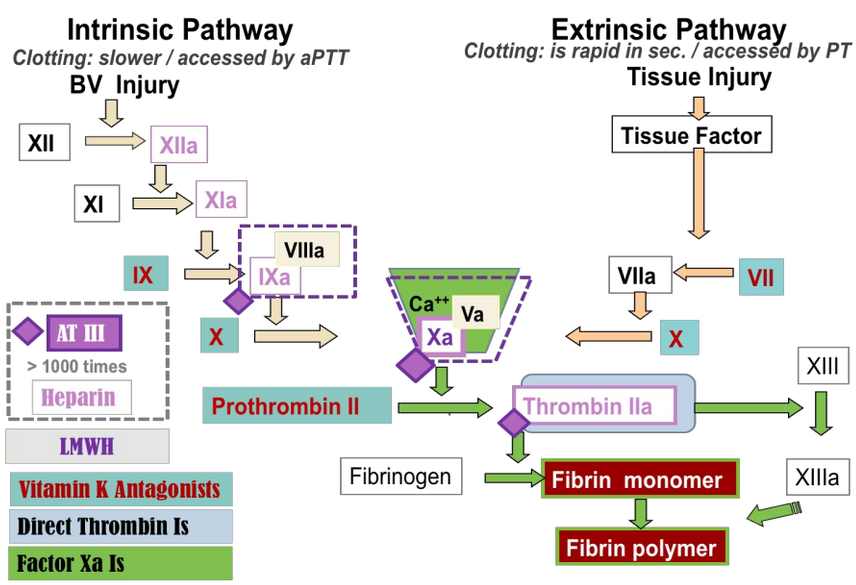
1a. ***Intrinsic pathway:** All clotting factors are within the blood (tissue factor=thromboplastin) less important for initial coagulation, more important for amplification

1b. ***Extrinsic pathway:** Initiating factor is outside the blood.

2. *Both converge to common pathway

3. *13 soluble factors are involved in clotting which normally circulate in an inactive state and must be activated to form a fibrin clot.

4. *Endogenous Inhibitors of Coagulation:



Coagulation cascade: is a sequence of interactions between proteins to cause fibrin deposition at the site of tissue injury

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.

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

Anticoagulants

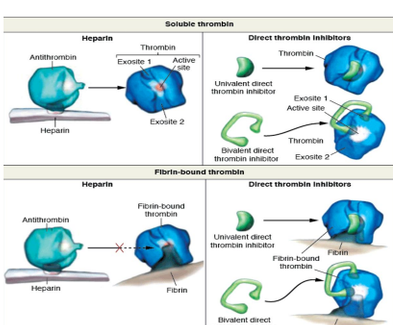
Parenteral				Oral
Act as thrombin inhibitors either in a direct way or indirect way				Act as Vitamin K antagonist (e.g. Warfarin)
Unfractionated heparin **(UFH)**	Low mol. Weight heparin **(LMWH)**	Factor Xa inhibitors	Direct Thrombin inhibitors	Vitamin K antagonists
3000-30000	< 800	Pentasaccharide		Coumarins*; Warfarin > 40 potency than Dicumarol *A family of drugs, including warfarin & Dicumarol. Dr: Just remember warfarin
Antithrombin III	> Xa	Xa	IIa	
	Enoxaparin Dalteparin	**Indirect:Fondaparinux** IR direct: Rivaroxaban R (Oral)	Bivalirudin R Lepirudin IR Argatroban R Dabigatran R (Oral)	

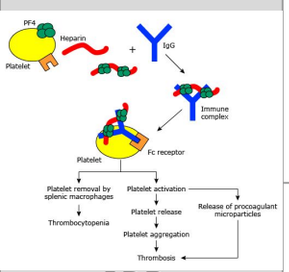
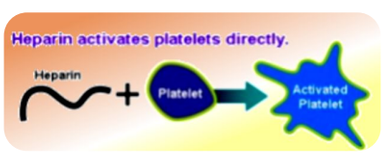
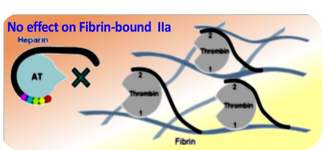
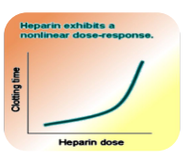
R=reversible, IR=irreversible

Anticoagulants indications

- Myocardial infarction (MI)
- Deep venous thrombosis (DVT)
- Peripheral arterial emboli, pulmonary embolism (PE) and many other conditions
- 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) • 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
M.O.A	• Hepar**in** acts ***indirectly*** by increasing the activity of the endogenous anticoagulant "antithrombin III" inactivate thrombin (essential for clot formation) and other serine proteases (clotting factors) e.g **VIIa**, **IXa** and particularly **Xa**, The anticoagulant effect of heparin is mediated via antithrombin III. • In the absence of heparin this inactivation is slow, when Heparin binds to antithrombin III **(heparin acting as a cofactor)**, 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. Dr explanation of the illustration:- -Top left panel: We can see heparin attached to antithrombin 3. Antithrombin 3 alone isn't really active but when it is paired with heparin the complex becomes 1000x more active to degrade thrombin and when thrombin is inactivated you don't have coagulation. -Bottom Left panel: Although the complex is still very active, thrombin doesn't have any active sites to offer because it is already bound to fibrin so the complex won't work. -Right panels: Direct thrombin inhibitors work on both free and fibrin bound thrombin. 

Limitations	• <u>No predictable anticoagulant effects;</u> inter-patient & intra-patient variability in response to a given dosage ⟶ in hospital setting, repeated monitoring • <u>Low bioavailability</u> ⟶ binds to plasma proteins, endothelium & macrophages (this is different for every patient which is why the dose is also different for each patient) • <u>Re-thrombosis</u> ⟶ activates platelets (since it's a large molecule, it can activate antigen antibody reactions) as it does not neutralize fibrin-bound IIa • UFH carries a risk of **heparin-induced thrombocytopenia (HIT)**: 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. - There are disorders that reduce the number of platelets, such as heparin-induced thrombocytopenia (HIT) that typically <u>cause thrombosis or clots, instead of bleeding.</u> - It happen in 4% pts. on heparin, latency 5-10 days after 1st exposure or 2-3 days. after re-exposures ⟶ Venous > Arterial thrombosis **if HIT happened:** - **Heparin discontinuation,** No packed platelets ⟶ More thrombosis - No warfarin (takes too long) ⟶ precipitate venous gangrene, **give** ⟶ **DTIs** (Direct thrombin inhibitor) - The need for regular monitoring (aPTT)
 **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-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
Limitations Pictures	  

Indirect Thrombin Inhibitors, cont.
Low-Molecular-Weight Heparins (LMWHs)

Drug	Heparin fragments (enoxaparin, dalteparin)	Synthetic pentasaccharide (fondaparinux)
MOA and uses	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 Used increasingly in place of unfractionated heparin.	
Advantages	• ↑ 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	

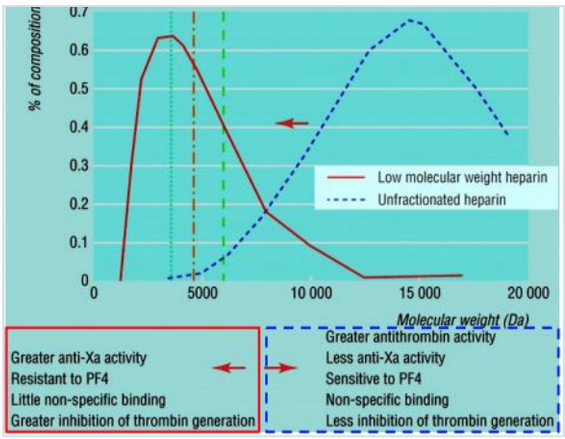
UF heparin and LMW Heparin

Important

The theoretical pharmacologic advantages of LMWH over UFH arise from the preferential binding ratio to factor Xa over thrombin.

LMWH (Enoxaparin , Dalteparin) have:

- Less plasma protein binding,
- Less platelet activation and lower risk of re-thrombosis and thrombocytopenia.,
- Good bioavailability
- More predictable response



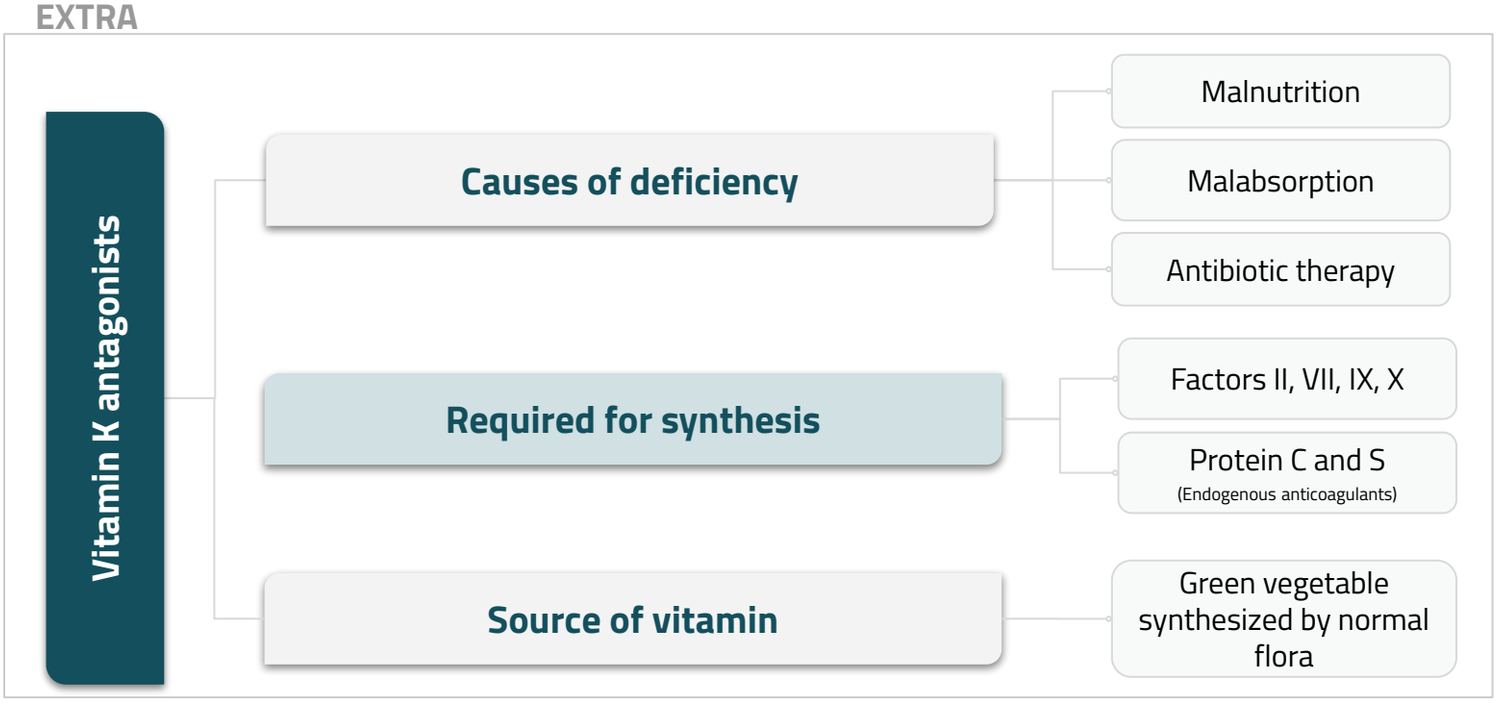
Not in the slides but Important

Differences between UFH and LMWH Heparins

	Heparin (UFH)	LMWH
IV ½ life	2 hours	4 hours
Bioavailability after SC injection	20%	90%
Non-specific binding	Greater	Little
Anticoagulant response	Variable	Predictable
Major adverse effect	Frequent bleeding, HIT, osteoporosis	Less frequent bleeding
Specific Antagonist	Protamine sulfate	Incomplete
Setting for Therapy	Hospital	Hospital & outpatient clinic
Laboratory Monitoring	Needed (aPTT)	Not needed
Anti-Xa activity	Less	Greater
Antithrombin activity	Greater	-
Inhibition of thrombin generation	Less	Greater Because of anti-Xa activity
PF4	Sensitive	Resistant No risk for thrombosis

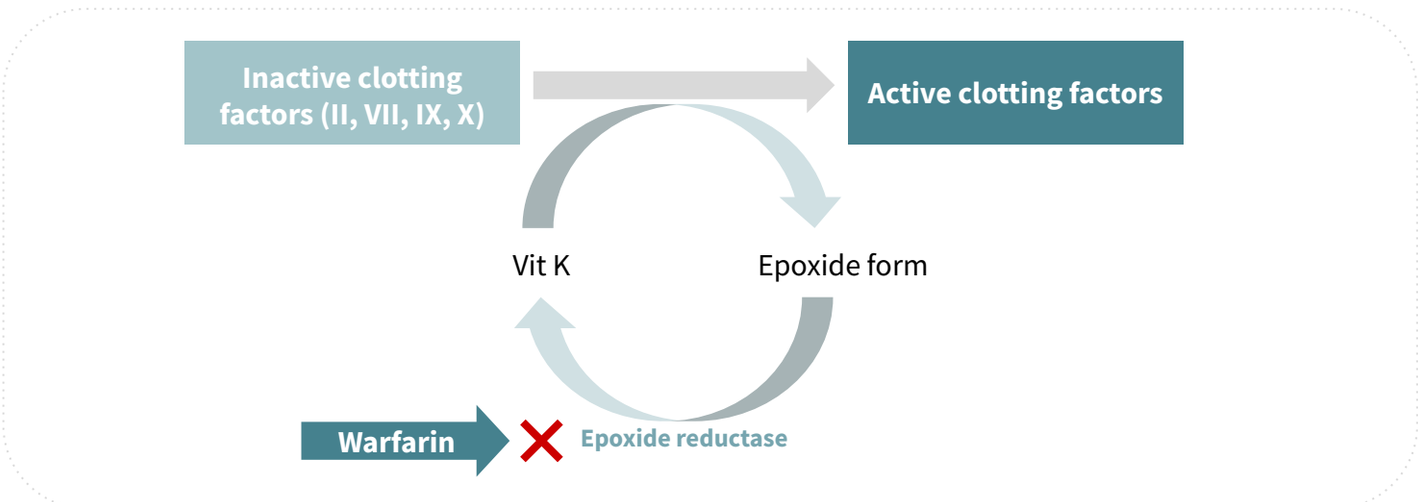
Oral anticoagulants
Vitamin K antagonists (Warfarin)

EXTRA



M.O.A of Warfarin

For better understanding, refer to Biochemistry of Vitamin K lecture



1. Precursors of factors II, VII, IX & X (1972) 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 oxidized Vit K has to recycle back to reduced form by Vit K epoxide reductase.

3. This enzyme is blocked by Vitamin K Antagonists → losing the coagulation factors the ability to function.

Oral anticoagulants Vitamin K antagonists, cont..

Drug	Coumarin (Warfarin)
M.O.A	• 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 <u>already-synthesized</u> coagulation factors**; therefore, the therapeutic effects are not seen until these factors are depleted. So it acts in liver only, NOT peripheral blood unlike heparin.
PK	1. 98% **bound to plasma proteins** (albumin)1 2. Monitoring anticoagulant effect of **warfarin by measuring PT**, which is expressed 3. as an **International Normalized Ratio (INR)** 4. **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 5. Warfarin **has a slow offset of action** due to the time required for synthesis of new functional coagulation factors
‹Limitations	• Wide variation in drug response • **Has narrow therapeutic window,** So any change in that level can be hazardous. • Slow onset of action, **so not in given in emergency conditions** • 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.
Drug interactions Mnemonic ↑ activity **(Splanch):** **S**alicylates **P**henylbutazone, **L**iquid paraffin **A**ntibiotics (oral) **N**SAIDs **H**eparin ↓ activity (**B rock**): **B**arbiturates **R**ifampicin **O**ral contraceptives **C**arbamazepine, **C**holestyramine, **C**olestipol **K** (Vitamin)	• **Increase Warfarin activity** 1. Inhibition of Vit. K synthesis by intestinal flora; **oral antibiotics** 2. Inhibition of <u>Vit K absorption</u>; **liquid paraffin** Remember Constipation drugs lecture? 3. Decrease in drug metabolism by microsomal enzyme inhibitors; **chloramphenicol, & cimetidine** Remember Cytochrome lecture? 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 <u>drug absorption</u> from GIT; **cholestyramine, colestipol** Remember #CVS? 2. Increase in synthesis of clotting factors; **Vit K, oral contraceptives** 3. Increase in drug metabolism by microsomal enzyme inducers; **Carbamazepine; barbiturates, rifampicin** Remember Cytochrome lecture?
Contraindication	★ **Pregnancy** as it **can cross the placental barrier** and cause abortion, hemorrhagic disorder in the fetus and birth defects → **give heparin or LMWH instead** (DOC)
Reverse warfarin action	If the patient develops bleeding due to Warfarin: • Stop the drug • IV injection of **vitamin K** • Fresh frozen blood

Factors that Alter the response to VIT K Antagonists

Factors increase the response:

1 Impaired synthesis of clotting factors

Hepatocellular disorders:
Hepatitis; infective or chronic alcoholism

2 Vitamin K deficiency

Inadequate diet:
- Malnutrition
- Dieting
- Decreased GI absorption

3 Increased catabolism of clotting factors

In hypermetabolic states;
as in fever, thyrotoxicosis

Factors decrease the response:

1 Decreased plasma protein binding[1]

↑ Elimination of free drug & shortening of its t ½
E.g patient with nephrotic syndrome (proteinuria)

2 Genetic

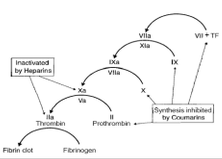
Hereditary resistance to oral anticoagulants

3 Decreased catabolism of clotting factors

Hypothyroidism

1) Normally 90% of warfarin is bound to proteins. If the binding is decreased, we will see an initial increase in activity followed by an increase in metabolism and elimination of warfarin

Comparison between Heparin and Warfarin

Drug	Heparin	Warfarin
Chemical nature	• Large polysaccharide, water soluble	• Small molecule, lipid soluble derivatives of vit k
M.O.A	• ↑ Activity of Antithrombin III, resulting in the inactivation of coagulation factors IIa ,IXa, Xa, XIa, XIIa. • Action in **vivo and vitro** • Rapid / variable 	• ↓ Hepatic synthesis of Vit K- dependent factors II, VII, IX, X, cournarins prevent their Gamma-carboxylation. • Has no effect on factors already present. • Action in **vivo only** • Slow / latency / variable
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 • **Placental access**
Monitoring	• Partial thromboplastin time (PTT) 1.5-2.5 times normal (30sec) • Clotting time 2-3 times normal (5-7 min)	• Prothrombin time (PT); expressed as International Normalized Ratio (INR)
Antagonist (Antidote)	• Protamine sulfate I.V (1mg/100 units UFH) (chemical antagonism, fast onset) • + Fresh blood	• ↑ Vit K cofactor synthesis (slow onset) • Fresh frozen plasma (fast onset) /fresh blood +needs de novo synthesis
Uses	• **Rapid anticoagulation (intensive,** emergency**) for:** Thromboses, emboli, unstable angina disseminated intravascular coagulation (DIC), open heart surgery ...etc	• **Long term anticoagulation (controlled,** prophylaxis**) for:** Thromboses, emboli, post MI, heart valve damage, atrial arrhythmias ...etc
Toxicity	• Bleeding • Osteoporosis • Thrombocytopenia (HIT) • Hypersensitivity	• Bleeding • Skin necrosis (if low protein C) • Drug interactions • Teratogenic (Bone dysmorphogenesis)

Summary

Drug	M.O.A	Uses	ADRs/ADV/DisA	C.I
Parenteral Anticoagulant				
Indirect Thrombin Inhibitors (Unfractionated heparin "UFH")				
Unfractionated heparin Rapidly Acting	It acts indirectly by increasing the activity of the anticoagulant antithrombin III which inhibits activated clotting factors mainly thrombin (factor IIa) and factor Xa Important note: heparin does not inhibit the clotting factors!	**Rapid anticoagulation (intensive, emergency) for:** Thromboses, emboli, unstable angina disseminated intravascular coagulation (DIC), open heart surgery ...etc ———————— **ANTIDOTE:** protamine sulfate	**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 (since it's a large molecule, it can activate antigen antibody reactions) as it does not neutralize fibrin-bound IIa • **heparin-induced thrombocytopenia (HIT)** - It happen in 4% pts. on heparin, latency 5-10 days. after 1st exposure or 2-3 days. after re-exposures → Venous > Arterial thrombosis *No warfarin (takes too long) → precipitate venous gangrene, **give → DTIs** (Direct thrombin inhibitor) - **Heparin discontinuation,** No packed platelets → More thrombosis	
Indirect Thrombin Inhibitors (Low-Molecular-Weight Heparins "LMWHs")				
Heparin fragments: **-enoxaparin** **-dalteparin** **Synthetic pentasaccharide (fondaparinux)**			**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. • **Much better tolerability;** - Given subcutaneously - ↓ Frequency of administration due to longer duration of action - ↓ Need for regular monitoring - Outside hospital settings	
Oral Anticoagulants				
Vit K Antagonist				
Warfarin Has delayed onset	Inhibits synthesis of Vitamin K-dependent coagulation factors II, VII, IX, & X as well as anticoagulant proteins C & S Vit K epoxide reductase antagonism	**Long term anticoagulation (Controlled)for:** Thromboses, emboli, post MI, heart valve damage, atrial arrhythmias ...etc ———————— **ANTIDOTE:** -Stop the drug -IV **injection of vitamin K** to ↑Vit k cofactor synthesis slow Onset -Fresh frozen blood (Fast onset)	**DISADVANTAGES: -** • Wide variation in drug response • **Has narrow therapeutic window,** So any change in that level can be hazardous. • Slow onset of action, **so not in given in emergency conditions** • 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.	**Pregnancy** as it **can cross the placental barrier** and cause abortion, hemorrhagic disorder in the fetus and birth defects → **give heparin or LMWH instead** (DOC)

MCQs

Q1: A 60-year-old male, following hospitalization for an acute myocardial infarction, is treated with warfarin. What is the mechanism of action of warfarin?			
A- Increase in the plasma level of factor IX	B- Activation of plasminogen	C- Binding of Ca 2+ion cofactor in some coagulation steps	D- Inhibits synthesis of Vitamin K-dependent coagulation factors
Q2: A 34-year-old man admitted to the emergency department with a presumptive diagnosis of pulmonary thromboembolism started a treatment that included a drug that acts by accelerating the binding between antithrombin III and clotting factor proteases. Which of the following drugs has this mechanism of action?			
A- Warfarin	B- Heparin	C- Alteplase	D- Clopidogrel
Q3:A 55-year-old man complained to his physician of red blood in his stools and pink urine. Two weeks earlier, the man had started a treatment with warfarin for recurrent deep vein thrombosis. On physical examination, the patient appears pale and diaphoretic. Vital signs were blood pressure 85/55 mm Hg, heart rate 105 bpm, respirations 20/min. An appropriate therapy was started. Which of the following drugs was most likely administered intravenously to the patient?			
A- Protamine sulfate	B- Vitamin K	C- Fresh frozen plasma	D- Alteplase
Q4: A 62-year-old woman complained to her physician of nose bleeds and red eyes. The woman had been receiving warfarin for 1 month because of deep venous thrombosis. Four days earlier, she had started treatment with erythromycin for acute pharyngitis. Which of the following drug-induced changes was most likely responsible for the patient's symptoms?			
A- Erythromycin-induced inhibition of warfarin metabolism	B- Warfarin-induced decreased of vitamin K production by intestinal flora	C- Erythromycin-induced decrease of intestinal absorption of vitamin K	D-Erythromycin-induced inhibition of warfarin metabolism
Q5: A 28-year-old woman who had had a mitral valve replacement for rheumatic heart disease 2 years ago had her suspected pregnancy confirmed by a positive pregnancy test. Her current medications include the anticoagulant warfarin (U.S. Food and Drug Administration [FDA] category for teratogenic risk (D) Which of the following would be the best course of action to be implemented by her family physician?			
A- Stop all medications throughout pregnancy	B- Replace warfarin with heparin	C- Continue warfarin	D- Reduce the dose of warfarin
Q6: A 45-year-old male post–myocardial infarction (post-MI) for one week is being treated with intravenous (IV) heparin. Stool guaiac on admission was negative, but is now 4+, and he has had an episode of hematemesis. The heparin is discontinued, and a drug is given to counteract the bleeding. What drug was given?			
A- Protamine sulfate	B- Vitamin K	C- Dipyridamole	D- Aminocaproic acid
Q7: A 67-year-old woman presented to the clinic because of progressive swelling and soreness of the left calf. After physical examination and lab exams, a diagnosis of deep venous thrombosis was made, and a treatment with enoxaparin was started. Which of the following is the main advantage of this drug over the standard unfractionated heparin?			
A- Complete absence of bleeding complications	B- Lower risk of re-thrombosis and thrombocytopenia	C- Less predictable response	D- Less bioavailability

1	2	3	4	5	6	7
D	B	B	A	B	A	B

SAQ

Q1) A 63-year-old man told his physician that in the morning he discovered his urine was cloudy and red. The man was suffering from persistent atrial fibrillation and had been stabilized on warfarin therapy for 1 month. Three days earlier, he had started taking an over-the-counter preparation containing cimetidine for heartburn.

a. **What's the MOA of warfarin?**
b. **Describe the effect of cimetidine on warfarin? List 4 drugs that can cause the same effect?**
c. **What test you'll be using to monitor his coagulation function?**
d. **List two possible consequences in the case of toxicity?**

Q2) A 34-year-old woman in her second trimester of pregnancy presented with a tender, red, swollen calf that was diagnosed as a deep vein thrombosis (DVT) and was treated successfully. However, because of the high risk of recurrence of the DVT, she was treated with an anticoagulant for the remainder of her pregnancy.

a. **The most appropriate drug for her condition is?**
b. **Mention its MOA?**
c. **What drug you should avoid? why?**

Q3) Anticoagulation is needed immediately in a 55 year old man with deep vein thrombosis. (Qa-c are about the same drug)

a. **What's the appropriate anticoagulant for his condition? Why?**
b. **What test you'll be using to monitor his coagulation function?**
c. **List four possible consequences in the case of toxicity?**
d. **What would you prescribe as a maintenance therapy for his condition?**

Q4) Compare between UFH and LMWH

Answers

A1) a. Inhibits synthesis of Vitamin K-dependent coagulation factors II, VII, IX, & X as well as anticoagulant proteins C & S,

b. **Increased warfarin activity** (by Decreasing drug metabolism by microsomal enzyme inhibitors), ↑ activity:Salicylates, Phenylbutazone, Liquid paraffin, Antibiotics (oral), NSAIDs, Heparin

c. Prothrombin time (PT); expressed as International Normalized Ratio (INR). d.Bleeding, Skin necrosis

A2) a. Heparin e.g. Enoxaparin

b. It acts indirectly by increasing the activity of the anticoagulant antithrombin III which inhibits activated clotting factors mainly thrombin (factor IIa) and factor Xa

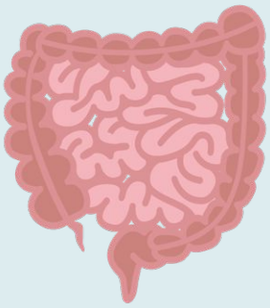
c. Warfarin, it can cross the placental barrier and cause abortion, hemorrhagic disorder in the fetus and birth defects.

A3) a. Heparin, because our other option "warfarin" has slow onset of action, so not in given in emergency conditions

b. Partial thromboplastin time (PTT) it should be 1.5-2.5 times normal (30sec) c. Bleeding, Osteoporosis, Thrombocytopenia (HIT), Hypersensitivity d. warfarin

A4) LMWH (Enoxaparin , Dalteparin) have: Less plasma protein binding, Less platelet activation and lower risk of re-thrombosis and thrombocytopenia., Good bioavailability, More predictable response

Feedback Form



Gastrointestinal Block

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- Yasmine Alqarni

Revisers

- Dana Naibulharam
- Mishal Althunayan
- Omar Alhalabi

Members

- Abdulaziz Alderaywsh
- Abdulaziz Alghuligah
- Abdulrahman Almebki
- Abdulrhman Alsuhaibany
- Aljoharah Albnyan
- Aljoud Algazlan
- Arwa alqahtani
- Feras Alqaidi
- Lama Alahmadi
- Maha Alanazi
- Manal Altwaim
- Mona Alomiriny
- Norah Almasaad
- Noura Bamarei
- Rand AlRefaei
- Rawan Bakader
- Salem Alshihri
- Shahd Almezel