Lecture 8

Anticoagulants

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.

- Additional Notes
- Important
- Explanation –Extra-

before starting, please check our GIT block correction

For any correction, suggestion or any useful information
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Drugs and coagulation

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

based on female`s slide

Anticoagulants

1-Indication:

Anticoagulants are indicated In:

- myocardial infarction.
- Deep venous thrombosis.
- peripheral arterial emboli
- pulmonary embolism
- Anticoagulants are also used in blood transfusions, and dialysis procedures.

2-Endogenous Inhibitors of Coagulation:

1-Anti-thrombin III: It inactivates thrombin and other coagulation factors **(IIa & Xa)** by forming complex with these factors. **Heparin** like molecules enhances these interactions.

2-Prostacyclin (PGI2): is synthesized by endothelial cells and inhibits **platelet aggregation**.

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

ATIII: work at factors **IXa, Xa, IIa.**
Heparin make **ATIII** strong like **a superman**

Vit K Antagonist : work at factors **IIa, VIIa, IXa, X**

DTIs: only act on **thrombin IIa**

Factor Xa Inhibitors: only work on factor **Xa**

Intrinsic Pathway

Clotting: slower / assessed by aPTT

BV Injury

XII → XIIa

XI → XIa

IX + VIIIa → IXa

X

AT III

> 1000 times

Heparin

LMWH

Vitamin K Antagonists

Direct Thrombin Is

Factor Xa Is

Extrinsic Pathway

Clotting: is rapid in sec. / assessed by PT

Tissue Injury

Tissue Factor

VII → VIIa

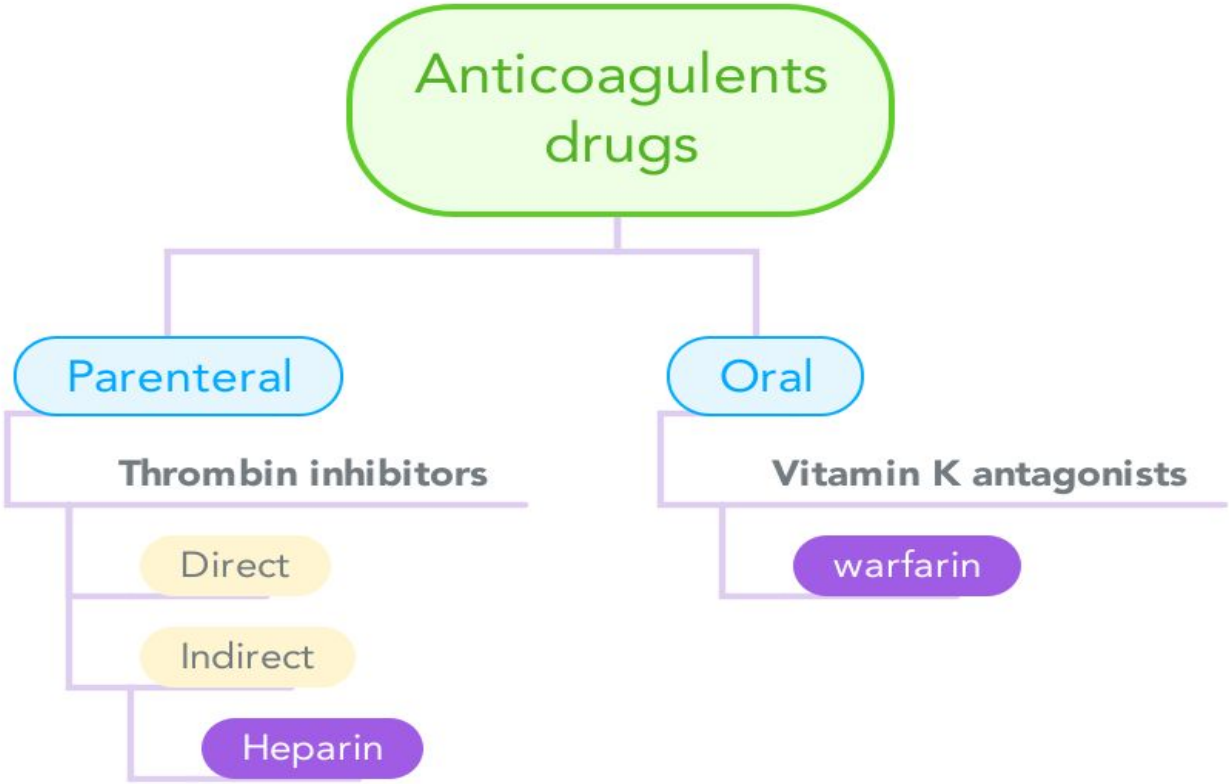
X

Ca^{++} + Va + Xa

Prothrombin II → Thrombin IIa

XIII → XIIIa

Fibrinogen → Fibrin monomer → Fibrin polymer


Anticoagulents drugs
Parenteral
Oral
Thrombin inhibitors
Vitamin K antagonists
Direct
Indirect
Heparin
warfarin

Heparin (Unfractionated Heparin)

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) and Xa***

★ Heparin binds to both **antithrombin III and thrombin** to form **a ternary complex → Heparin dissociates leaving the thrombin bound to its inhibitor→ heparin dissociate to bind another anti-thrombin**

pharmacokinetics

- **It should be administered by IV or SC injection.** Not injected IM as it causes **haematomas** at injection site
- **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.**
- **Low bioavailability , it binds to plasma proteins, endothelium & macrophages**

therapeutic uses

- **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**

disadvantages

- **The need for regular monitoring (aPTT)**
- **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**

Heparin (Unfractionated Heparin)

heparin induced thrombocytopenia:

There are reduce the number of platelets that typically cause thrombosis, or clots, instead of bleeding.

MANAGEMENT: **Heparin discontinuation +** Give **Direct thrombin inhibitors**.

adverse effect	1-The major adverse effect of heparin is **bleeding** 2-**Allergic reactions** (chills, fever, urticaria) as heparin is of animal origin and should be used cautiously in patients with allergy 4-Long-term heparin therapy is associated with ***osteoporosis*** 5-**heparin induced thrombocytopenia**
contraindications	• **Bleeding disorders, hemophilia** • **Patients with hypersensitivity to the drug** • **Recent surgery of the brain, eye or spinal cord, threatened abortion**
Antidote	**protamine sulfate**

lower molecular weight heparin (LMWH)

drugs	Enoxaparin	Dalteparin
MOA	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	
advantage over UFH	★ it works on factor Xa and it don't work on thrombin IIa ★ The convenience of once- or twice- daily subcutaneous injections without regular coagulation monitoring. ★ More predictable response ★ Long plasma half-life and improved bioavailability ★ Less plasma protein binding ★ Less platelet activation and lower risk of re-thrombosis and thrombocytopenia	

	factor Xa inhibitor	direct thrombin inhibitor
drugs	**Fondaparinux**	**hirudin, Lepirudin**
MOA	• a synthetic heparin compound that inhibits factor Xa by antithrombin but does not inhibit thrombin	• DTIs exert their anticoagulant effect by direct binding to thrombin • This direct effect is rapid and potent
advantage	• can be given once a day at a fixed dose without coagulation monitoring • Less likely than UFH or LMWHs to trigger HIT	DTIs are not associated with the development of thrombocytopenia

vitamin K antagonist

Drugs	Warfarin
MOA	• Inhibits synthesis of Vitamin K-dependent coagulation factors II, VII, IX, & X as well as anticoagulant proteins C & S • Does not have an effect on already-synthesized coagulation factors; therefore, the therapeutic effects are not seen until these factors are depleted • 3-4 days until effect is seen
Limitation	• 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 (2C9) 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 pregnancy give heparin or LMWH instead

vitamin K antagonist (warfarin)

Factors altering response to vit. K antagonist:

1-Inadequate diet; malnutrition, dieting, decreased absorption

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.

Decrease response:

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 anticoagulant

Drugs modulating response to vit k antagonists:

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

so increase its t½

4. Displacement of the drug from protein binding sites;

- phenylbutazone & salicylates

5. Co-administration of drugs that increase bleeding tendency by;

- inhibiting platelet function; NSAIDs
- inhibiting coagulation factors; heparin

summary from kaplan USMLE step 1 book

COMPARATIVE PROPERTIES OF HEPARIN AND WARFARIN

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	Heparin catalyzes the binding of antithrombin III (a serine protease inhibitor) to factors IIa, IXa, Xa, XIa, and XIIa, resulting in their rapid inactivation	↓ Hepatic synthesis of vitamin K–dependent factors II, VII, IX, X—coumarins prevent γ-carboxylation by inhibiting vitamin K epoxide reductase; no effect on factors already present. *In vivo* effects only
Monitoring	Partial thromboplastin time (PTT)	Prothrombin time (PT); INR
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)

MCQs

1. The primary advantage of enoxaparin over heparin is that is:

A. more effectively Inhibits the synthesis of clotting factors
B. does not cause thrombocytopenia
C. has a longer half-life

2. Which one of these drugs is a direct thrombin inhibitor:

A. Enoxaparin
B. Rivaroxaban
C. Lepirudin

3. Pregnant lady has deep vein thrombosis , she has to take anticoagulant.. Which drug is safe to her?

A. Warfarin
B. Heparin/LMWH
C. NSAIDS

4. The MOA of Vitamin K antagonist is:

A. Inactivation of Thrombin 2a
B. Inhibition of Factor Xa
C. Decrease Synthesis

5. A 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

6.80 years patient has Myocardial infarction, he can't go to the hospital .. Which drug is more effective and suitable for his situation ?

A. Heparin
B. Warfarin
C. LMWH

1.c
2.c
3.b
4.c
5.b
6.c

Good luck!

Done by Pharmacology team 434

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For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com