Pharmacology

HLS

Sheet No. 5

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Anticoagulants, Thrombolytics, and Antiplatelet Drugs

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Lecture 5

Original text is black, what the doctor added is in this color

Good luck

Modified *by*: *Ahmad AlHurani*

Lepirudin

- **Hirudin is derived from Leech.**
- **Lepirudin is from recombinant DNA technology.**
- **Irreversible inhibitor, inactivates fibrin-bound thrombin.**
- **Used IV or SC.**
- **Monitored by aPTT.**
- **Eliminated by hepatic metabolism and renal excretion, accumulates in renal failure.**
- **Used for thrombosis related to HIT.** or thrombosis **DUE TO HIT**
- **No antidote is available.**

and the circulating thrombin but to a lesser extent. MAINLY:Fibrin-bound thrombin

synthetic rather than recombinant DNA

Bivalirudin

- **Bivalirudin is a direct thrombin inhibitor.**
- **It is a synthetic congener of the naturally occurring anticoagulant hirudin.**
- **Used IV.**
- **Elimination half-life is ~ 25 min.**
- **Cleared by hepatic and renal elimination and proteolytic cleavage.**
- **It inhibits both circulating and clot-bound thrombin, reversibly.**
- **Thus, it has less bleeding risk than other r-hirudins.**

Bivalirudin

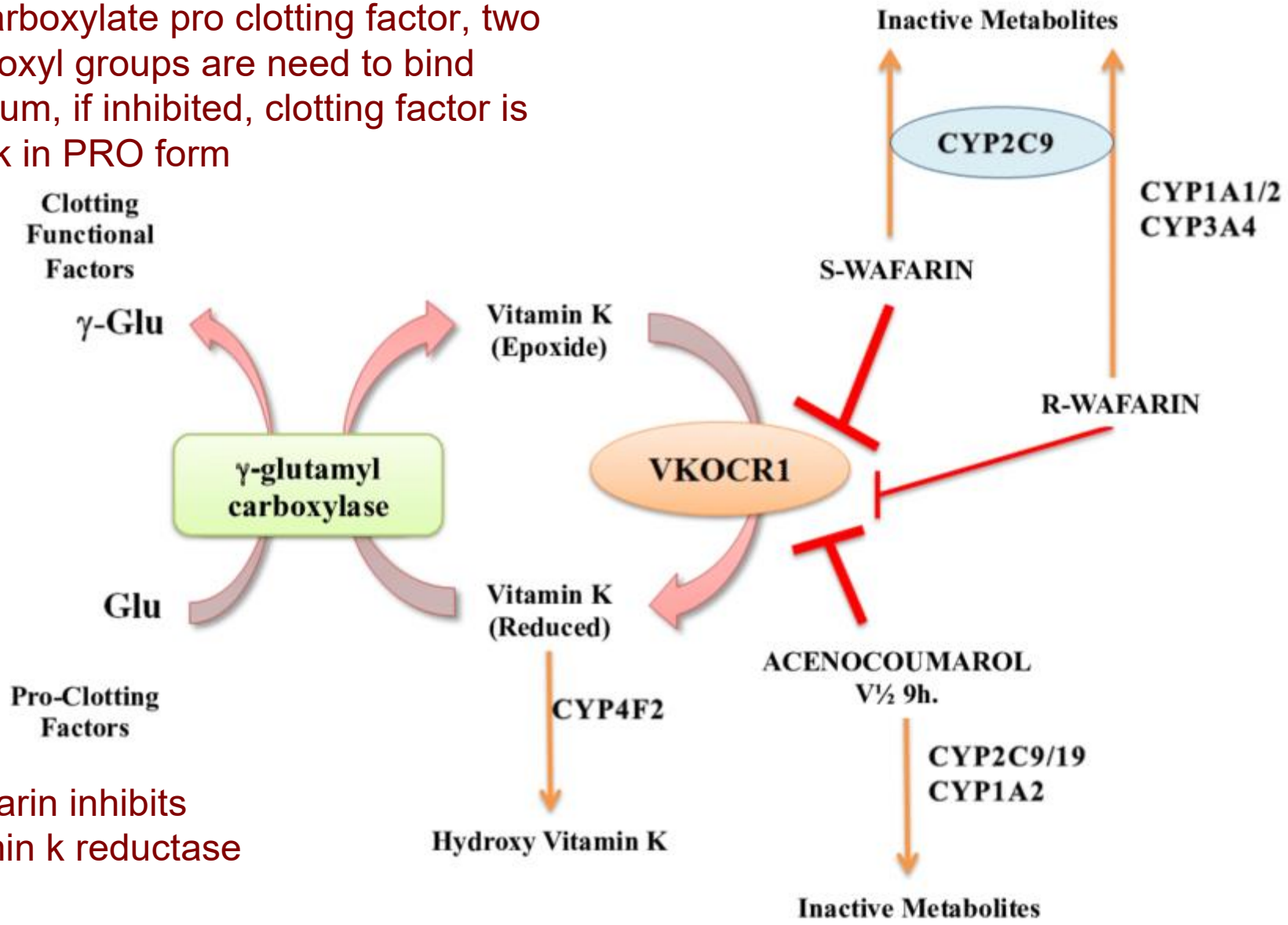
- It also inhibits thrombin-mediated platelet activation and aggregation.
- Used in percutaneous coronary intervention (PCI) and for HIT.
- Monitored by “thrombin inhibitor assay” which is better than aPTT because it is NOT affected by antiphospholipid antibodies.
- It is contraindicated in severe renal impairment.
- Thrombin inhibitor assay (It's like saying anti IIa activity)

ischemic heart disease

Warfarin

- **Vitamin K in its reduced form is a required cofactor for vitamin K-dependent carboxylation of factors II, VII, IX, and X, as well as the endogenous anticoagulant proteins C and S; which is required for their biologic activity.**
- **Warfarin inhibits the reduction of vitamin K epoxide, reducing the formation of complete functioning clotting factors.**
- **It has NO effect on preformed clotting factors, thus, full antithrombotic effect is NOT achieved for at least 6 days after warfarin therapy initiation.**

Vitamin K in the reduced form is needed to carboxylate pro clotting factor, two carboxyl groups are need to bind calcium, if inhibited, clotting factor is stuck in PRO form



Warfarin inhibits vitamin k reductase

Warfarin

- **The time required for warfarin to achieve its pharmacologic effect is dependent on coagulation protein elimination half-lives (6 hours for factor VII and 72 hours for prothrombin).**
- **Full antithrombatic effect is not achieved for at least 6 days after warfarin therapy initiation**

Half-Lives (hours)

Clotting Factor	
II	72
VII	6
IX	24
X	40
Protein C	8
Protein S	30

-We have 2 reasons why we can't give heparin alone
1) delayed action (by already formed clotting factors
2) possibility to develop thrombosis starting with warfarin alone
-Protein C, a natural anticoagulant, has short half life, so at the beginning of administration, we might have thrombosis, as we lost a natural anticoagulant; protein C
-We deal with this by starting our thrombosis treatment regiment with heparin, but as it's uncomfortable for the patient (IV), we love to switch to the oral warfarin, but we shouldn't stop heparin for warfarin, we have to make an overlap in which we are giving the patient both drugs at the same time.
-2 ways are possible:
1) Give both drugs together from the start, after 5 days you switch to warfarin only.
2)Treat 5 days with heparin alone, then overlap both together for 5 days, then switch to warfarin alone.
Both give the same results.

there's an overlap between toxic and therapeutic dose (therapeutic for x patient, toxic for y patient)

Warfarin

- **Because of its narrow therapeutic index, predisposition to drug and food interactions, and exacerbation of bleeding, warfarin requires continuous patient monitoring and education to achieve optimal outcomes.**
- **As it's highly protein bound (drug-drug interactions), and it's metabolized so affected by inhibition/ induction of metabolism, vitamin K containing food antagonize warfarin, multivitamins that include vitamin K antagonize it too.**

Warfarin

Adverse Effects: all are possible

1. **Bleeding (mild to life threatening).**

- **Vitamin K is the antidote, can be given parenteraly or orally; the oral route is preferred in the absence of serious bleeding.**
- **In case of bleeding, warfarin should be temporarily stopped or the dose reduced.**

2. **“Purple toe syndrome” is thought to be the result of cholesterol microembolization into the arterial circulation of the toes.**

Warfarin

warfarin-induced thrombosis that causes skin necrosis that's why we overlap heparin too | it's due to protein C

3. **Warfarin-induced skin necrosis (due to thrombosis) in the first week of therapy (starts as a painful maculopapular rash and ecchymosis or purpura that progresses to necrotic gangrene).**

- **Areas of the body rich in subcutaneous fat are most commonly affected (breasts, thighs, buttocks, and abdomen).**
- **Monitored by prothrombin time - PT, this test requires monitoring in the same lab, or you can use standardized PT aka INR - international normalized ratio, that allows us to compare between results.**
- **INR must be prolonged to have anticoagulant effect (preferably 2-3 times normal PT and depending on the severity of the thrombosis)**

INR+ = enhances warfarin effect = more antithrombatic effect
INR-=reduces warfarin effect=less antithrombatic effect

Warfarin Drug–drug Interactions

Pharmacodynamic Interaction	Mechanism
ASA/NSAIDs	Antiplatelet, GI injury
Clopidogrel/TIclopidine	Antiplatelet
Tramadol	INR elevation (mech. Unknown) more bleeding
Levothyroxine	Increased catabolism of clotting factors
Vitamin K containing food/Supplements	INR reduction (reverse warfarin mechanism of action)

Drug–drug Interactions:

- Other anticoagulant, thrombolytics, antiplatelet agents, aspirin, NSAIDs, dipyridamole, or sulfinpyrazone enhance bleeding risk.

INR Elevation	increases warfarin effect
Amiodarone	cvs
Fluoroquinolones	antibiotic
Trimethoprim/sulfamethoxazole	antibiotic
Metronidazole	antiparasitic, antibiotic
Azole antifungals	
Statins	cholesterol -
Isoniazid	
NSAIDs	
Sertraline	
Gemfibrozil	cholesterol -
Ethanol	
Macrolides	
Cimetidine	H2 blocker, - acid secretion
Omeprazole	PPI, - acid secretion
Fluorouracil	

INR Reduction	reduces warfarin effect
Rifampin	anti TB
Barbiturates	anti epileptic
Carbamazepine	anti epileptic
Phenytoin	
St John's wort	reduces drug metabolism
Cigarette smoking	
Charcoal broiled food	
Cholestyramine (Bile acid binding resins)	warfarin will not be absorbed
Oral contraceptives (Estrogens)	

Open this site or link to see tables for more comprehensive description of drug and food interactions with warfarin, if you like.

https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/486574

Pharmacogenomics

The variation in warfarin and it's effects makes it a bad drug that scientists tried to find alternatives for

- **CYP2C9 is the hepatic microsomal enzyme responsible for metabolism of the more potent S-enantionmer of warfarin.**
- **Polymorphisms in CYP2C9 and the gene coding for VKOR (Vitamin K epoxide reductase) explain a substantial proportion of warfarin dose variability between patients.**
- **Poor metabolizer subtypes have been associated with increased risk of bleeding.**
- **Warfarin resistance can be due to mutations in the receptor gene.**
- **For individualized warfarin dosing consult (www.warfarindosing.org).**

warfarin is indirect as it does its effect by vitamin k epoxide reductase

Direct Oral Anticoagulants

all of those oral anticoagulants are directed to replace warfarin
direct: work on clotting factors themselves

(DOACs):

- 1) Rivaroxaban, apixaban, and edoxaban are potent and selective inhibitors of both free and clot-bound factor Xa. Free and clot bound Xa
- They do not require antithrombin to exert their anticoagulant effect. both groups (1+2), all of these drugs are reversible too
- 2) Dabigatran (prodrug) is a selective, reversible, direct factor IIa inhibitor.(needs metabolism first)
- These drugs are partially eliminated by the kidney to various extent, and should be used with caution in patients with renal dysfunction. reduced dose in renal dysfunction

partially by kidney means that it's eliminated by liver too (2 main organs of elimination)

Direct Oral Anticoagulants

- **Terminal half-lives ~10 hours for the Factor Xa inhibitors, and 16 hours for dabigatran.** Used to determine frequency of administration
- **Rivaroxaban and apixaban are substrates of cytochrome CYP3A4, and P-glycoprotein.**

Indications:

1. **The Xa inhibitors rivaroxaban and apixaban can prevent venous thromboembolism (VTE) following hip or knee replacement surgery.** prophylaxis before surgery (prevention)
2. **Dabigatran, rivaroxaban and apixaban can be used for extended VTE treatment after the first 6 months of anticoagulant therapy.**

both groups

Direct Oral Anticoagulants

Adverse Effects:

1. Gastrointestinal complaints. nausea, vomiting, abdominal pain
2. Bleeding which ranges from minor – severe & fatal.

- Discontinuation of therapy and supportive management.

  (You don't give the next dose)

- Activated charcoal may provide some benefits if drug intake occurred within 2 hours of presentation, and dabigatran is hemodializable. Activated charcoal binds the drug in the intestine and prevent it's absorption (within 2 hours because it'll be completely absorbed after 2-3 hours usually)
  hemodializable: if patient was given dabigatran and developed bleeding, hemodialysis will get rid of the drug - غسيل الكلى

Direct Oral Anticoagulants

- Idarucizumab rapidly reverses the dabigatran anticoagulant effect following IV administration.
- It binds to dabigatran and its acylglucuronide with higher affinity than that of dabigatran to thrombin, that'll free the thrombin thus allowing it to exert its function as a clotting factor again stopping the bleeding
- It is used in life-threatening bleeding and when there is need for urgent surgical intervention.
- Routinely, we'll use activated charcoal and hemodialysis for bleeding that's not life threatening

Direct Oral Anticoagulants

Drug–drug and Drug–food Interactions:

- DOACs are P-gp substrates and subject to changes in anticoagulant effect when coadministered with P-gp inhibitors or inducers.
- Rivaroxaban and apixaban are subject to interactions involving inhibitors or inducers of CYP3A4.
- Other anticoagulant, thrombolytics, antiplatelet agents, aspirin, NSAIDs, dipyridamole, or sulfinpyrazone enhance bleeding risk.