HEMATOLOGY
&LYMPH SYSTEM

Pharmacology sheet

Number	3
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In the previous lecture:

- We talked about the anticoagulant Heparin, which is an old drug with many problems, the main problem is associated with the heterogeneity of the drug, so patients have to go under laboratory monitoring in order to give them the right dose and avoid adverse effects as much as we can.

– But as we said it's so problematic to do laboratory monitoring to each patient !! so that lead scientists to make what we called fractionated heparin (low molecular weight heparin), which is a homogenous drug that could be given to the patients with suspected response.

**The fractionated Heparin don't need any monitoring except in three cases that we talked about:

1-patients with renal failure 2- obese patients 3- pregnancy

**We talked about renal failure issue, LMW heparin is removed by renal excretion while the full heparin is excreted through the bile so we don't adjust the heparin dose in renal failure patient but we have to do so in term of LMWH as we said previously.

** We ended with important point which is "heparin induced thrombocytopenia", which could happen in both Heparin and LMWH (some books say that the incidence is lower in LMWH, but we have to monitor the level of thrombocytes in both cases)

** So we have to put an eye on the platelet count before and after giving the drug, by make a baseline of platelet count and then do it again after 3-5 days (duration of the reaction).

**There is an antidote for heparin named protamine sulfate, keep in mind that it only acts on full non fractionated Heparin, however it does not really bind well with LMW heparin because protamine is discovered and designed to the full heparin and since we make LMW heparin it's no longer can bind it!! So one of the main disadvantages of LMWH is that it does not have an antidote (some people use protamine sulfate as an antidote for LMWH but it isn't right)

protamine is used to neutralize heparin by binding to it.

Protamine is a medicine that requires a high level of caution when used (keep in mind drug-drug interaction).

**Heparin is a hospital drug since it is administrated subcutaneously, and because of that the patient can't stick with it for a long time so we need to find an oral anticoagulant drug.

Let's introduce our oral anticoagulants:

Warfarin

-Warfarin is the oldest and the most used anticoagulant drug.

-It's a real problematic drug, it is one of the most difficult drugs to deal with since its associated with several side effects that make the patient need hospitalization.

- Warfarin has a narrow therapeutic window (although is isn't as narrow as that of digoxin)

-There are multiple factors that interact with and affect warfarin like food, drugs and normal flora.

Mechanism of action:

It affects and inhibits the coagulation directly by blocking carboxylation of factors VII, IX, X, II (the most important are X and II) in addition to protein C & S. This blockade results in incomplete molecules that are biologically inactive in coagulation.

- This carboxylation is physiologically coupled with the oxidative deactivation of vitamin K.

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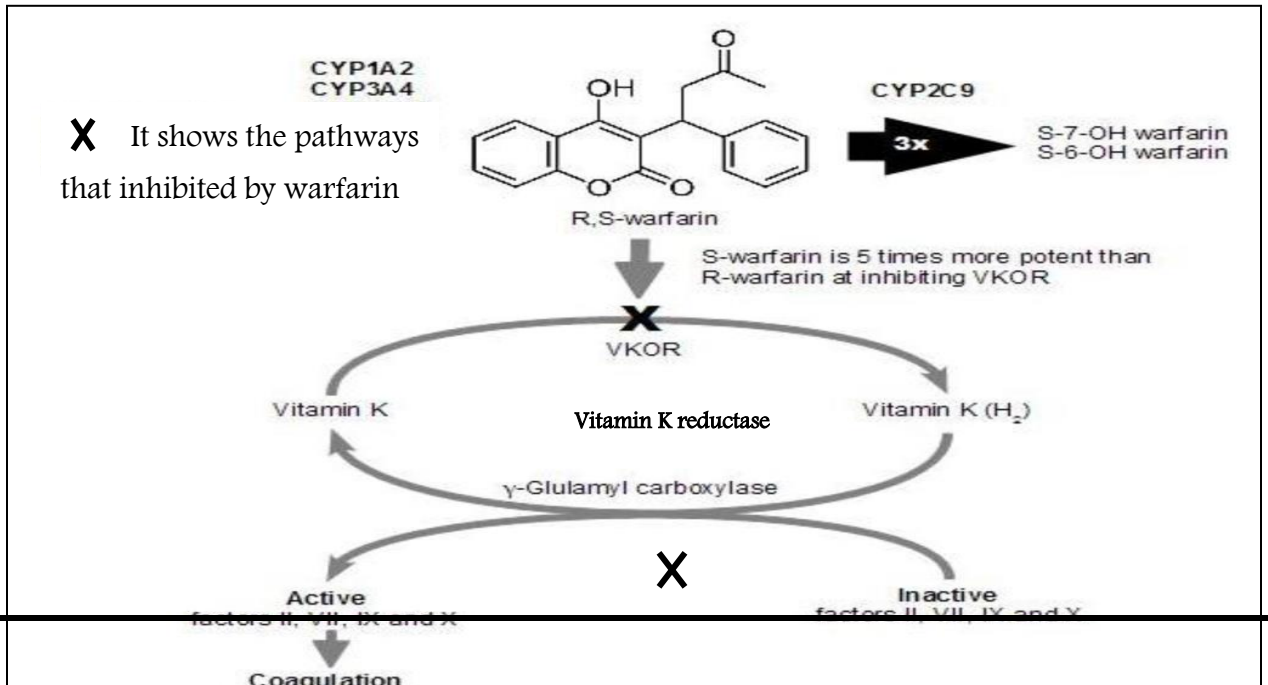
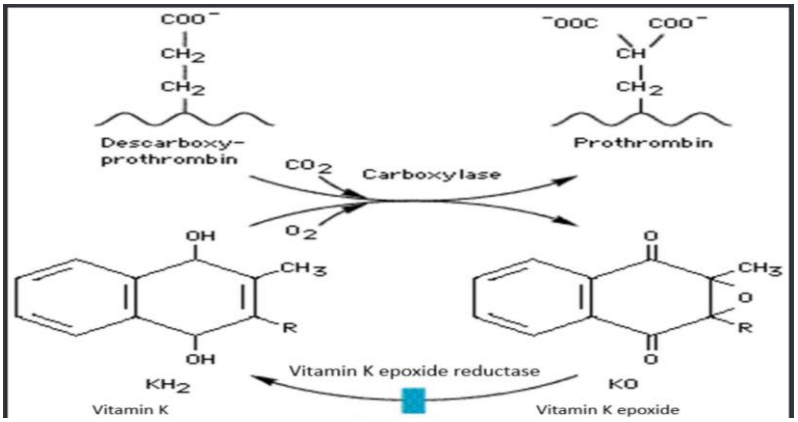


-In normal situations, coagulation factors are present in an inactive form (decarboxylated form) so if we need to activate them, we must carboxylate them using the enzyme carboxylase, but in order to make this reaction possible, it must be coupled with oxidative reaction of vitamin K (vitamin K is a cofactor), which is converted to vitamin K epoxide (inactive form of vitamin K), which must be reduced again by vitamin k epoxide reductase to return to its functional form in order to be coupled again with carboxylase enzyme and so on.

-Warfarin is an inhibitor to vitamin K epoxide reductase enzyme, so vitamin K is trapped in its inactive form, and thus the carboxylation reaction can't take place, so by that we are inhibiting the activation of coagulation factors.

The carboxylation process is associated with the vitamin K cycle. In this cycle, vitamin K is reduced by enzyme Vitamin K reductase to its hydroquinone form, vitamin KH2, which then catalyzes the carboxylation process and is converted to its epoxide (vitamin KO). This is then converted back to vitamin K by the enzyme Vitamin KO reductase.

**I added this note to help in understanding.



Vitamin K is the antidote of warfarin, so if the patient has bleeding because of warfarin we use vitamin K to drive the reaction forward and stop the bleeding.

Just to remember LMW heparin doesn't have antidote

So when we prescribe warfarin for the patient, we advise him to avoid types of food that are rich in Vitamin K (parsley, spinach, tomatoes, coriander)

- Vitamin K epoxide reductase has a problem, the gene that codes for this enzyme is very polymorphic (single nucleotide polymorphism is common), 25% of the population have a change in the binding site where warfarin binds.

So if we have normal patient A and patient B with polymorphism in this enzyme, and we give them warfarin, the binding of warfarin in the patient B will be lower than patient A, so it will not be that effective, also the action of this polymorphic enzyme will differ in comparison to the normal activity and that's why we find variations among the patients.

Another reason for these variations, Warfarin is metabolized (inhibited) through the enzyme CYP2C9 (remember Clopidogrel is activated through CYP2C19 enzyme), warfarin will go to the liver and it will undergo deactivation (since it's a drug not a prodrug) by the action of CYP2C9 which has two problem:

1- single nucleotide polymorphism (either in one allele or the two alleles)

2- CYP2C9 can be induced or inhibited, even food can alter its activity (like chamomile, ginger, Capsicum)

So the dosage of warfarin will be different between patients.

*How to monitor Warfarin?

Unlike heparin, the heterogeneity is among the patients not the drug itself, since the variation depends on food habits and activity of the enzymes (CYP2CP and vitamin epoxide reductase) and all the variants that we have discussed.

So we have to monitor the patients on warfarin by what we called INR

(the doctor talked very quickly about INR and he didn't make it clear, so I tried to summarize it in few points)

-We monitor warfarin activity by INR.

-INR (international normalized ratio) is a type of PT (prothrombin time) assays.

-We perform INR on glass or in test tube without adding factors (unlike aPTT).

-Normal PT is about 50 to 60 seconds.

-INR is used to normalize the differences in PT values that may result from using different kits and devices.

-The target INR for warfarin is 2-3 (this is important to know)

Extra: The **prothrombin time** (**PT**)—along with its derived measures of **prothrombin ratio** (**PR**) and **international normalized ratio** (**INR**)—are assays evaluating the *extrinsic pathway* of coagulation. This test is also called "ProTime INR" and "PT/INR". They are used to determine the clotting tendency of blood, in the measure of warfarin dosage, liver damage, and vitamin K status. PT measures factors I (Fibrinogen), II (Prothrombin), V (Proaccelerin), VII (Proconvertin), and X (Stuart–Prower Factor). It is used in conjunction with the activated partial thromboplastin time (aPTT) which measures the *intrinsic pathway* and common pathway. (source :Wikipedia)

Links for more information

https://healthengine.com.au/info/INR-Test

https://labtestsonline.org/understanding/analytes/pt/tab/test/

- Warfarin affects a lot of proteins like protein C & S, prothrombin, factor X, etc. We used to know that these factors have different half-life values, and the longest half-life is for factor II which is about 50-60 hours. The problem is that protein C has a very short half-life which is about 6-8 hours, so when we give warfarin to the patient, it will inhibit the carboxylation of all these factors (protein C, factors II, X, VII, IX), and since protein C has the shortest half-life, its activity will decline firstly. We know that protein C is an anti-coagulant, so when we inhibit its activation, this will cause coagulation (the opposite of our desired effect). So keep in mind that when you give warfarin there is a period with high risk of thrombosis until we reach the full activity of the drug(this is a side effect).

How to deal with this problem? Bridging therapy: **heparin or enoxaparin must be overlapped** with warfarin & continued for 4–5 days until an **INR between 2.0 and 3.0** is reached.

In order to get the full activity of warfarin, all existing factor II must be cleared. So if we calculate it we need about 7 days, but in reality we need about 3-5 days to get rid of the activity of thrombin (factor II), so until we reach the full activity of warfarin, and to prevent any coagulation that might happen due to the decreased activity of protein C, we combine heparin with warfarin (bridging therapy). During this time, we must monitor both

heparin and warfarin (we must measure both aPTT and INR, the target aPTT should be between 2-2.5 and the target INR should be between 2-3) so when we reach the target INR (when we expect that warfarin has reached its full activity) we withdraw heparin.

Q: a patient suffers from heparin induced thrombocytopenia

and Thrombosis, is it acceptable to give him warfarin?

The answer is absolutely NO !!, since warfarin will cause thrombosis in the first 3 days because of the reduction in the activity of protein C.

Warfarin drug interactions:

1- pharmacokinetic mechanisms:

a. enzyme induction and inhibition (CYP2C9).

b. decrease plasma protein binding. 99% of warfarin is bound to albumin so it may be displaced by another drug that has higher binding affinity to the same binding site of warfarin on albumin, so the patient may suffer from bleeding.

From the slide: azapropazone displaces warfarin from plasma proteins and inhibits its metabolism.

2- pharmacodynamic mechanisms:

a. synergism (impaired hemostasis) if we combine warfarin with heparin, aspirin or any anticoagulant drug.

b. competitive antagonism, like Vitamin K if the patient is taking warfarin and eats any food rich in vitamin K.

NOTE: using of drugs that interact with warfarin is not absolutely contraindicated to warfarin (in some cases you may use them)

- these tables are not for memorizing, but you should read them to be familiar with some drugs and to know that there are a lot of drugs that affect the action of warfarin.

I. Drugs that ↑ prothrombin time		
↓ warfarin metabolism		
Allopurinol Cimetidine Omeprazole Phenytoin (sometimes) Phenylbutazone Azapropazone Amiodarone	Ethanol (acute) Disulfiram Metronidazole Ketoconazole Fluconazole Miconazole	Erythromycin Azithromycin Ciprofloxacin Norfloxacin Sulfonamides
↑ catabolism of clotting factors		
	Thyroid hormones	
↓ synth. of clotting factors (↓ bacteria & direct inh. of epoxide reductase)		
Cefamandole Cefotetan	Cefmetazole Cefoperazone	
Unestablished mechanisms		
Acetaminophen?	Fibrates Statins	Corticosteroids Androgens

II. Drugs that ↓ prothrombin time		
↑ synthesis of clotting factors		
Estrogens	Vitamin K	
↓ catabolism of clotting factors		
Methimazole	Propylthiouracil	
Induction of warfarin metabolism		
Carbamazepine Phenytoin (usually)	Barbiturates Ethanol (chronic)	Griseofulvin Rifampin
↓ absorption of warfarin		
Cholestyramine	Colestipol	Sucralfate
Unestablished mechanism		
Azathioprine	Cyclosporine	Cyclophosphamide
↑ risk of bleeding without effect on PT		
Aspirin NSAIDs	Ticlopidine Clopidogrel	SSRIs

- Many herbal products have potential interactions – increased bleeding may occur:

1- capsicum pepper 2- garlic 3- ginger 4- gingko

5- ginseng 6- feverfew

- Some of vitamin K is produced by GIT flora, so if we take broad spectrum antibiotic, it will kill these flora leading to low vitamin K production and this will cause warfarin toxicity and bleeding.

- INR of patients with warfarin must be checked monthly, so if we found that INR=5 or more then we have to stop warfarin and give the patient Vitamin K for a duration of time, then we reintroduce warfarin to him slowly (start with a small dose and increase it slowly), we also give Vitamin K when the patient's blood has high fluidity without bleeding.

- But if the patient suffers from bleeding and his INR=5 or more (life threatening situation), we must stop warfarin and we don't give him Vitamin K, we give him fresh frozen plasma transfusion and factors.

- We give the patient fresh frozen plasma transfusion & IV vitamin K when INR>8 (more details in the 5^{th} year).

Extra: A unit of **fresh frozen plasma** (FFP) contains all coagulation factors. FFP is indicated for patients with a coagulopathy who are bleeding or at risk of bleeding, and where a specific therapy or factor concentrate is not appropriate or unavailable.

Warfarin Toxicity:

1- bleeding (the most dangerous)

2-venous thrombosis due to decreased activity of protein C.

3- Warfarin crosses the placenta readily & can cause hemorrhagic disorders & abnormal bone formation **in the fetus**. Thus, warfarin should never be administered during pregnancy. (you can prescribe warfarin during breastfeeding since it isn't excreted in breast milk).

-Warfarin is teratogenic (category X)

Extra: category X: do not use in pregnancy. Risks involved outweigh potential benefits. Safer alternatives exist.

The drug of choice for pregnant women is LMW Heparin.

4- purple toe syndrome, caused by cholesterol microembolization leading to arterial obstruction. People who eat a lot of meat and have hyperlipidemia have small emboli that stick on their blood vessels, so when we give anticoagulant like warfarin for years,

with time it will increase blood fluidity causing these emboli to detach from blood vessels and go through blood circulation, and since they are small they will stick in the small vessels like toe arteries and obstruct them, leading to ischemia, and that's why the toe appear purple in color (this side effect happens mostly with warfarin since the patient stick with it for a long time).

Finally, because of Warfarin complications, they try to discover and make new drugs that target specific factors. Ex: Dabigatran (pradaxa)

The problem of dabigatran (paradaxa) that it costs about 100Jd, while warfarin costs 3Jd.

Dabigatran (paradaxa)

Mechanism of action of Dabigatran: it is a direct thrombin inhibitor which inhibits:

- Both free and fibrin-bound thrombin
- Cleavage of fibrinogen to fibrin
- Thrombin-induced platelet aggregation

Onset: 1 hour (since it is a direct inhibitor), delayed by food

Antidote: FDA Approves Praxbind® (idarucizumab), Specific Reversal Agent for Pradaxa® (dabigatran etexilate) 2015. (it is a new antidote)

Another problem of dabigatran that we cannot monitor it (aPTT is not really efficient in monitoring).

Adverse effects: bleeding and dyspepsia (same as warfarin, but onset of action is faster, and it doesn't inhibit protein C and thus doesn't cause coagulation)

Indications (same as warfarin), examples:

-Atrial fibrillation

-DVT

-Pulmonary embolism

More details in the next lecture.

Sorry for any mistake, if there is any one please let me know