HEMATOLOGY
&LYMPH SYSTEM

Pharmacology sheet

Number	4
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In the previous lecture :

We were talking about warfarin so let's talk about it in general :

- **warfarin** is an anticoagulant drug that may cause thrombosis within the first days of its use because it has an **inhibitory effects on protein C & S** (which are endogenous anti-coagulants), this inactivation last for 5 days until warfarin become fully active after this period (specifically after get rid from thrombin which has a longer half-life than protein C & S) and we learned why such an action occur.

- we also talked about how to overcome this side effect, by using **bridging therapy** with heparin, by giving heparin for 3-5 days with warfarin then complete the therapy with warfarin only.

- warfarin is oral anticoagulant, its dosage is affected by the variation between patients and we learned that even the eating habit have a role in this variation.

- Warfarin also may cause major bleeding (and may be life threat situation that need hospitalization) like other anticoagulant drugs, so they start to search for another Alternatives and the first one we talked about is Dabigatran (paradaxa).

Anti-coagulants (continuation)

Dabigatran (paradaxa)

- it is a direct **thrombin inhibitor** (does not interfere with synthesis or activation of coagulation factors) which inhibit:

1- Both **free** and **fibrin-bound thrombin.**

2- Cleavage of **fibrinogen** to **fibrin.**

3- **Thrombin-induced platelet aggregation**.

- Onset: **1 hour** (since it is a direct inhibitor) very fast action comparing with warfarin. It has the advantage over warfarin since it not affected by eating habit (it actually affected but not that serious like warfarin) , it need 1 hour top give an action unlike warfarin and **doesn't need bridging therapy**.

- dabigatran (paradaxa) costs about 100Jd, while warfarin costs 3Jd.

Remember within all the patients who use anticoagulant drugs, about 5% will suffer from major bleeding.

***since** Dabigatran is not an exception from that side effect (major bleeding), researchers discovered an **antidote** for it that approved recently in 2015 by FDA which is **Praxbind** (idarucizumab), Praxbind is specific reversal agent that control this side effect of Pradaxa.

- the antidote for **warfarin** is **Vitamin K.**
- the antidote for **heparin** is **protamine sulfate**
- the antidote for Dabigatran is **Praxbind**.

*Adverse effects of Dabigatran (Paradaxa):

- Bleeding(8% to 33%; major bleeding ≤ 6%)

- dyspepsia (abdominal symptoms) that happens with about 11% of the patients.

-Note: Dabigatran is a substrate of **P-glycoprotein** (you need to be careful about drug-drug interactions)

-Note: we monitor Dabigatran depending on the aPPT (activated partial thromboplastin time).

Rivaroxaban

- it's an anticoagulant drug, onset: 2-4 hours and have an action on factor **Xa**.

- doesn't have an antidote yet.

- it could be used for short term, but it is more favorable to use dabigatran..

*Adverse effects :

1- **pruritus** (2%).

2- **bleeding**: DVT prophylaxis 6% (major <1%), Arterial fibrillation 21% (major about 6%).

3- **Thrombocytopenia** 3%, since its affect factor Xa.

4- **increase in liver enzyme** (3% - 7%)

Note: **Apixaban** is more effective and favorable than dabigatran & Rivaroxaban, its **specific direct Xa inhibitor**.

*Clinical Scenario: a patient has Heparin induced thrombocytopenia (**HIT**), what medication should we give him?

At first we **avoid** giving these drugs and stop them if under use: **Heparin** (since it's the main source of the problem), **LMW heparin**, heparin injectable derivative **Fondaparinux** (5 kDa) and **warfarin** (because it causes thrombosis initially). We **can** give them Hirudin, lepiridum, dabigatran and Rivaroxaban (almost all the drugs mentioned in slide 15 **except** Heparin, Heparin derivatives, Fondaparinux and warfarin, you don't have to memorize all drugs mentioned in slide 15).

*we finished talking about anticoagulant drugs

Thrombolytic Drugs (Fibrinolytics)

- drugs used in emergency, very effective in dissolving thrombi.

-**MOA**: they convert **plasminogen** to **plasmin** which will cause thrombi to dissolve by the degradation of **Fibrin**. Acute bleeding may occur, the patient must be monitored since those drugs have serious adverse effects that may result in death.

- we give these drugs **intravenously (IV)** for:

1- Multiple pulmonary emboli.
2- **Central deep venous thrombosis** (superior vena cava syndrome, ascending thrombophlebitis of iliofemoral vein, femoral vein blockage).
3- Acute myocardial infarction.
4- **Acute ischemic stroke:** t-PA should be used within 3 hours after onset of symptoms.

- we also can give them **Intra-arterially (IA)** for:

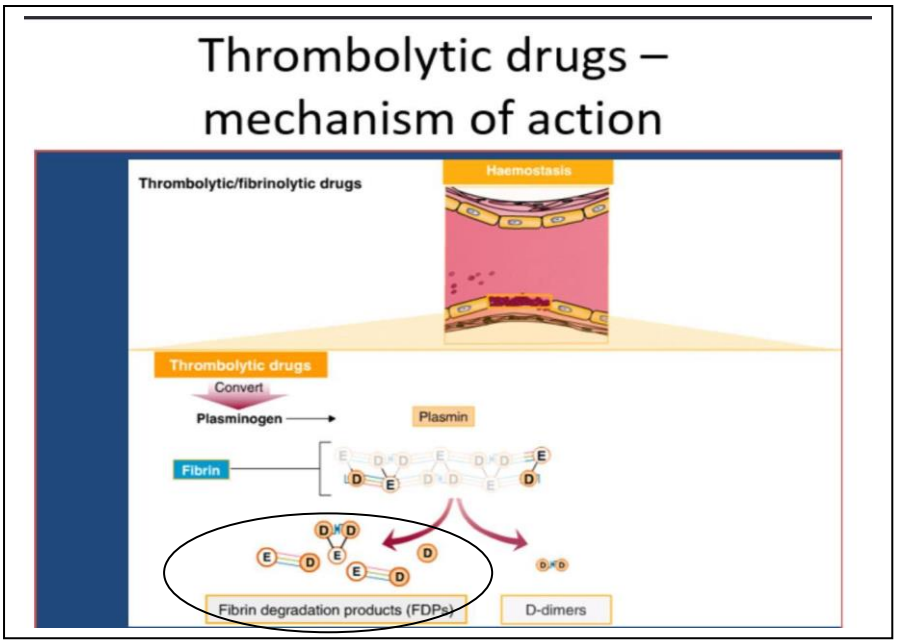
Peripheral vascular disease, where there is a blockage in peripheral arteries.

-the risk of giving a drug intra-arterially is higher than giving it intravenously since it enters the circulation faster.

- these drugs cannot differentiate between **protective hemostatic thrombi** and **target pathogenic thromboemboli**, both will be a target of thrombolytic drugs.

- these drugs degrade the circulating fibrinogen, causing bleeding.

*However, these drugs differ in their selectivity to plasminogen in clot & circulating plasminogen.



- Fibrin degradation products (FDPs) are produced from fibrin that degraded by plasmin, useful in diagnosis.

- these drugs are:

1- **streptokinase**: is an old drug (no longer used generally, but still used in Jordan), as its name imply it's taken from streptococci (bacterial product), it may cause allergic because of its bacterial origin.

* If it administrated one time you can't give it within the next three to six months because the body will have antibodies against streptokinase, which will cause allergic reactions.

* **MOA**: it combines with **plasminogen** forming a **complex** that is able to cleave another plasminogen molecules to plasmin, so it will convert all the plasminogen in the blood to plasmin, active plasmin will circulate in the blood affecting fibrin all over the body (we expect serious side effect since it’s not specific to pathologic clots).

- its produces more side effects than t-PA.

- Very strong and effective drug with serious adverse effects.

2- **Anistreplase**: an acetylated streptokinase-plasminogen complex that cleaves plasminogen to plasmin

3- **Urokinase**: a human enzyme synthesized by kidney, directly cleaves plasminogen to plasmin

4- **t-PA** (Tissue plasminogen activator): it's an endogenous direct activator of plasminogen it **preferentially** activate plasminogen that is bound to fibrin, meaning that it confines fibrinolysis to formed thrombi (in theory, but it still affects hemostatic thrombi), but unlike streptokinase it is more specific to formed thrombi than circulating plasminogen.

- it's given by infusion every 30 minutes, its half-life is 10 minutes.

* t-PA is more favorable drug than streptokinase since it is more selective.

5- **Alteplase**: is recombinant t-PA.

6- **Reteplase**: genetically-modified recombinant.

-Less expensive than t-PA but **less fibrin-selective.**

7- **Tenecteplase**: genetically-modified recombinant t-PA -> long t1/2

-**Slightly more fibrin-selective than t-PA** (means less side effects)

* As the clot dissolves, concentration of **thrombin will increase locally** leading to increase **platelet aggregation and formation of new thrombi**, specifically after the function of the thrombolytic drug ends.

- of course we have to avoid such unwanted side effect by giving anti platelet drugs of-course after stop giving the thrombolytic drug.

* the earlier the thrombolytic is given the better, for example if we have a patient with emboli and has myocardial infarction if he present to you after 6 hours you **can't** give him any thrombolytic (the damage happened already and we will only worsen the situation by giving thrombolytics), in the other hand if he present to you after an hour you better give him thrombolytics as soon as possible.

Side effects:

1- **Bleeding**, happens because these agents don't distinguish between the fibrin in unwanted thrombus & fibrin in a beneficial hemostatic plug or fibrinogen in the circulation.
2- **Reperfusion arrhythmia**, mostly in the heart (myocardial infarction) where the coronary artery is block, after treat it with thrombolytic the Perfusion to the heart will increase (suddenly) leading to arrhythmia.
3- **Hypotension**.
4- **Hypersensitivity**, with streptokinase and anistreplase.

Management

- Monitor IV sites for bleeding, redness and pain.

- Monitor for bleeding from gums, mucous membrane, nose and injection sites.

- Observe for signs of internal bleeding (decreased BP, restlessness, increased pulse).

Anti-Thrombolytic Drugs

Drugs that enhance thrombi formation by inhibiting the thrombolytic pathway. Therefore, they are used to treat bleeding conditions.

Aminocaproic Acid

- it **inhibits** enzymes like **plasmin** that responsible for **fibrolysis**, so its effective in treatment of certain bleeding disorders.

- it's an old drug, marketed as **Amicar**.

- used in postpartum bleeding, post major-surgery bleeding (colonectomy).

- Adverse effects: renal failure, edema, headache, malaise.

- Aminocaproic Acid is useful in enhancing hemostasis when fibrinolysis contributes to bleeding, In life threatening situations, transfusion of appropriate blood products and other emergency measures may be required.

Tranexamic acid

- Inhibits enzymes like plasmin that responsible for fibrolysis, can be given orally, IV, IM.

Uses:

1-Tranexamic acid has been found to **decrease the risk of death in people who have significant bleeding due to trauma** Its main benefit is if taken within the first three hours.

2-it is used to treat **heavy menstrual bleeding**. When taken orally it is treats regularly occurring heavy menstrual bleeding safely and effectively.

3-Dentists may give it as a wash (it will be one of its contents) to **stop gum bleeding** or (Aminocaproic Acid can be used) .

Note: Tranexamic acid is the only non-hormonal medicine that is FDA approved for heavy monthly bleeding.

*__Common adverse effects include__:
Headaches (50.4 - 60.4%), Back aches (20.7 - 31.4%), Nasal sinus problem (25.4%)

*Tranexamic acid is more expensive than Aminocaproic Acid.

*__Don't__ give these two drugs to patients with high risk of thrombosis(stroke, myocardial infarction, hypercholsteremia, , arteriosclerosis…) Or patients who are allergic to these drugs.

Iron Deficiency Anemia

- Results from insufficient iron intake (strict vegetarians), inability to absorb iron and iron loss because of bleeding.

- Its develop in vegetarian patients, patient who have colonectomy, heavy menstrual bleeding, pregnancy and breastfeeding.

- people with higher iron requirements are more susceptible to iron-deficiency anemia.

- hemorrhoids related to high dose aspirin may cause iron loss.

*How to treat IDA?

By giving them oral **iron supplement**, Three types of ferrous iron are typically prescribed: **ferrous sulfate, ferrous fumarate,** and **ferrous gluconate**.

- the most important and the best one is **ferrous sulfate** since it has ferrous more than the others but it has higher adverse effects.

-Ferrous sulfate contain **50-60%** iron.

-Ferrous gluconate contain 37% iron.

-Ferrous fumarate contain 13% iron.

Adverse effects of these supplements: Gastric distress, nausea, vomiting, dyspepsia and abdominal cramps and constipation. (side effects increase with the amount of iron given)

- the Iron found in the meat (Heme-iron) is more beneficial than iron in the plants (non-Heme-iron), because its absorbed more effectively.

- in patients who **can't** handle iron supplement like: who are bleeding in the gastrointestinal (GI) tract, inflammatory bowel disease and celiac disease,…….
we give them **IV iron** for 3-4 weeks.

Can be given IM once a month.

- heavy menstrual bleeding, pregnancy and breastfeeding women are the most group that need iron supplement (increased requirements).

- if the patient had an overdose he will suffer from iron toxicity especially in **children**, (iron supplements look like candies so children might eat them, causing them to develop iron toxicity which may cause death).

- we treat iron toxicity by giving an antidote called **deferoxamine** (iron-chelating agent), cleaning the iron from the blood, If this fails then dialysis is the next step.

- chronic iron toxicity occur in patients of blood transfusion and dialysis, we treat them with iron-chelating agents.