بسم الله الرحمن الرحيم

Pharmacology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

Final | Lecture 3 (pt.2)

Thrombolytics (Fibrinolytics)

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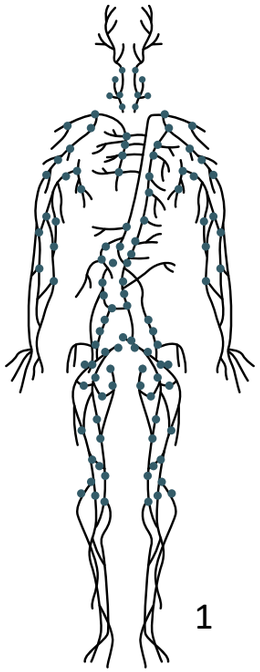

Thrombolytics (Fibrinolytics)

- **Thrombolytic agents** are drugs that rapidly **dissolve formed clots (thrombi).**
- They work by **converting plasminogen** into **plasmin**, an active enzyme that **breaks down fibrin,** the structural framework of blood clots. This process, known as **fibrinolysis**, leads to clot dissolution and restoration of normal blood flow.
- They are administered depending on the type of disease, within 6 hours in cases of ischemic stroke, but in myocardial infarction (MI) patients, there is usually a longer therapeutic window.

- They are mainly categorized into **3 categories:**

1. Streptokinase
2. Urokinase
3. t-PA (tissue plasminogen activator), alteplase, tenectplase & reteplase.

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Alteplase (the most important drug in this class) is a tissue plasminogen activator (**tPA**) that is **naturally produced** in the body. It can be manufactured using recombinant DNA technology. By **modifying the amino acid structure** of alteplase, scientists have developed **tenecteplase** and **reteplase**, which have longer half-lives and are easier to administer. **Tenecteplase also has greater fibrin specificity than alteplase, while reteplase has lower fibrin affinity** but better clot penetration, however, the latter 2 aren't available in our country yet.

- Streptokinase and urokinase are the old guys of the fibrinolytics.
- t-PA is the best and the most expensive (you will know the reason in a while).

Thrombolytics (Fibrinolytics)

- **Both protective** hemostatic **thrombi &** target **pathogenic thromboemboli** are **broken down.**
  - **Circulating** fibrinogen will be degraded, besides the fibrinogen in the clot → **Bleeding** can occur.
  - However, these drugs differ in their **selectivity** to plasminogen in **clot** & **circulating** plasminogen.

The Main side effect

- The **aim** of thrombolytic therapy is to **specifically** target plasminogen bound to the fibrin **clot**, rather than circulating plasminogen in the plasma. Targeting circulating plasminogen would lead to systemic fibrinolysis and excessive bleeding, which is a major adverse effect.
- Accordingly, **tPA** (including alteplase), tencteplase and reteplase are the most **fibrin-specific agents** (with varying degrees between them)*, as they primarily activate plasminogen bound to the **clot**. In contrast, **streptokinase and urokinase are non-fibrin-specific**, meaning they activate both circulating and clot-bound plasminogen, which increases the risk of systemic fibrinolysis and bleeding.
- The order of fibrin specificity among the three (Tenecteplase > Alteplase > Reteplase).

Thrombolytics (Fibrinolytics)

- **Indications**:

- **IV** for:

-**Multiple pulmonary emboli**

-**Central deep venous thrombosis** (eg, superior vena caval syndrome, ascending thrombophlebitis of iliofemoral vein).

The most important

-**Acute myocardial infarction**

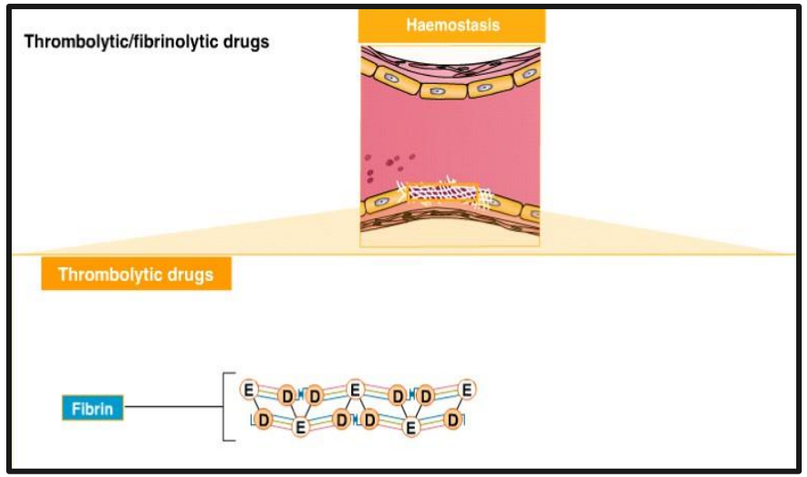
-**Acute ischemic stroke**: tPA should be used within 3 to 6 hours after onset of symptoms.

- **Intra-arterially** for:

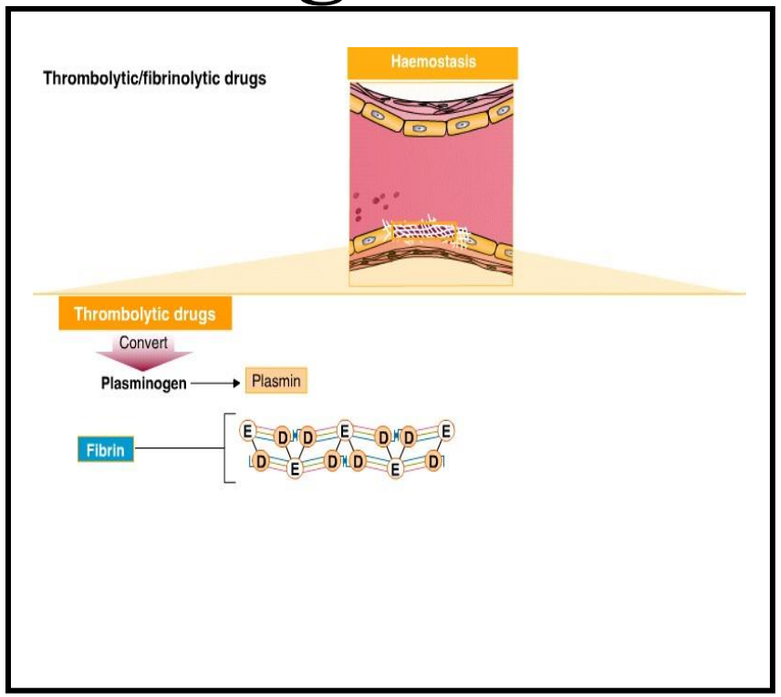
-Peripheral vascular disease →

- Intra-arterially could be dangerous under certain conditions due to bleeding.
- Our main aim is to dissolve the thrombi wherever they are.

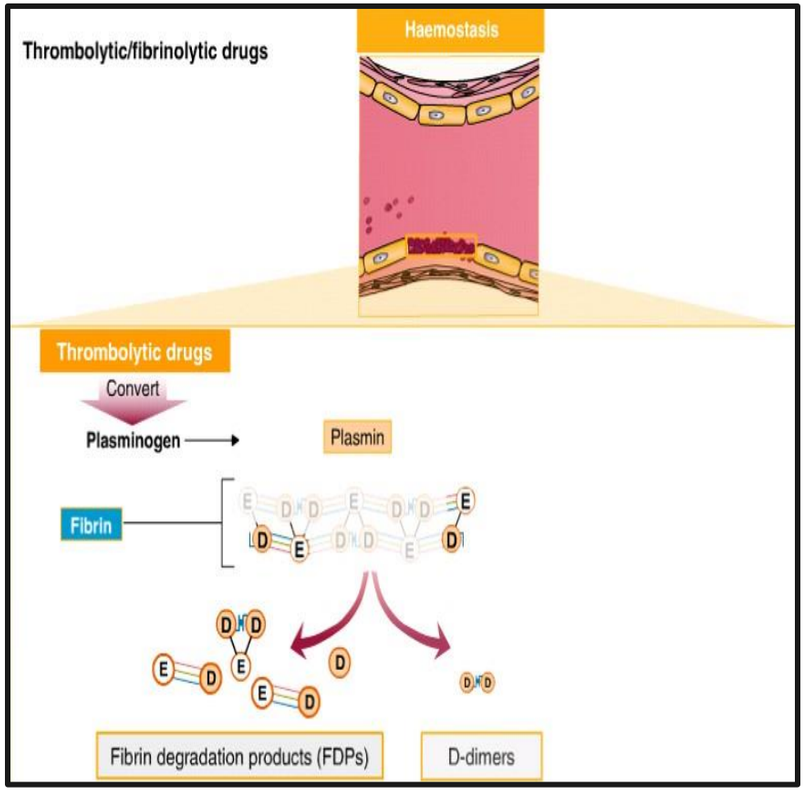
Thrombolytic drugs – mechanism of action



- When fibrinogen (the soluble precursor of fibrin) is converted to fibrin, it's made up of three pairs of polypeptide chains – two D regions and one E region in the middle: D – E – D
- During clot formation, these fibrin molecules become cross-linked by Factor XIIIa to make a stable clot.



- The drug converts plasminogen into active plasmin



- Plasmin breaks down the fibrin into fibrin degradation products & D-dimers.
- D-dimers are specific fragment that contains two D domains that remain cross-linked together
- D- dimers are considered as a clot degradation marker.

D-dimer is used as a biomarker to assess the extent of coagulation and fibrinolysis in COVID-19 patients. Elevated D-dimer levels indicate increased clot formation and breakdown, and are associated with disease severity and poor prognosis.

Thrombolytic drugs – mechanism of action

Note: The doctor said he will ask about the information starting from point 4

1. **Streptokinase**: combines with plasminogen. The complex cleaves another plasminogen molecule to plasmin.
2. **Anistreplase**: an acetylated streptokinase-plasminogen complex that cleaves plasminogen to plasmin.
3. **Urokinase**: directly cleaves plasminogen to plasmin.
4. **t-PA**: an **endogenous direct** activator of plasminogen. It **preferentially** activates **plasminogen that is bound to fibrin**. This, in theory, **confines fibrinolysis to formed thrombi.**
5. **Alteplase**: recombinant t-PA. (Most commonly used since it's cost-effective) .
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. (The best in terms of selectivity)

- The drugs 1,2 and 3 aren't preferred as they cause excessive bleeding because they target both the circulating and the clot plasminogen.

Thrombolytic drugs- Adverse Effects

- **Streptokinase** is formed by streptococci.
- **Urokinase** is a human enzyme synthesized by kidney and taken from the human urine.

- **As the clot dissolves** (as a result of using these drugs), **concentration of thrombin ↑ locally→ ↑ platelet aggregation & ↑ formation of new thrombi.**
- **→Give an antiplatelet or anticoagulant to prevent thrombosis.** **(As a prophylactic measure)**
- **The earlier the thrombolytic is given the better.**
- **Side effects:**

1) **Bleeding**: happens because these agents do not distinguish between the fibrin in an unwanted thrombus & fibrin in a beneficial hemostatic plug, or fibrinogen in the circulation.
2) **Reperfusion arrhythmia** : Occurs because cardiac cells are rapidly reoxgenated and nourished following a period of ischemia. If the thrombus is in the coronary artery is dissolved, a sudden influx of oxygen and nutrients reaches the ischemic cells. This abrupt change can disrupt cellular ion balance leading to arrhythmias as the cells adjust to the rapid restoration of blood flow.
3) **Hypotension.** So the blood pressure should be monitored, the doctor justified the adverse effect by “blood escapes into many other compartments”.

Thrombolytic drugs- Adverse Effects

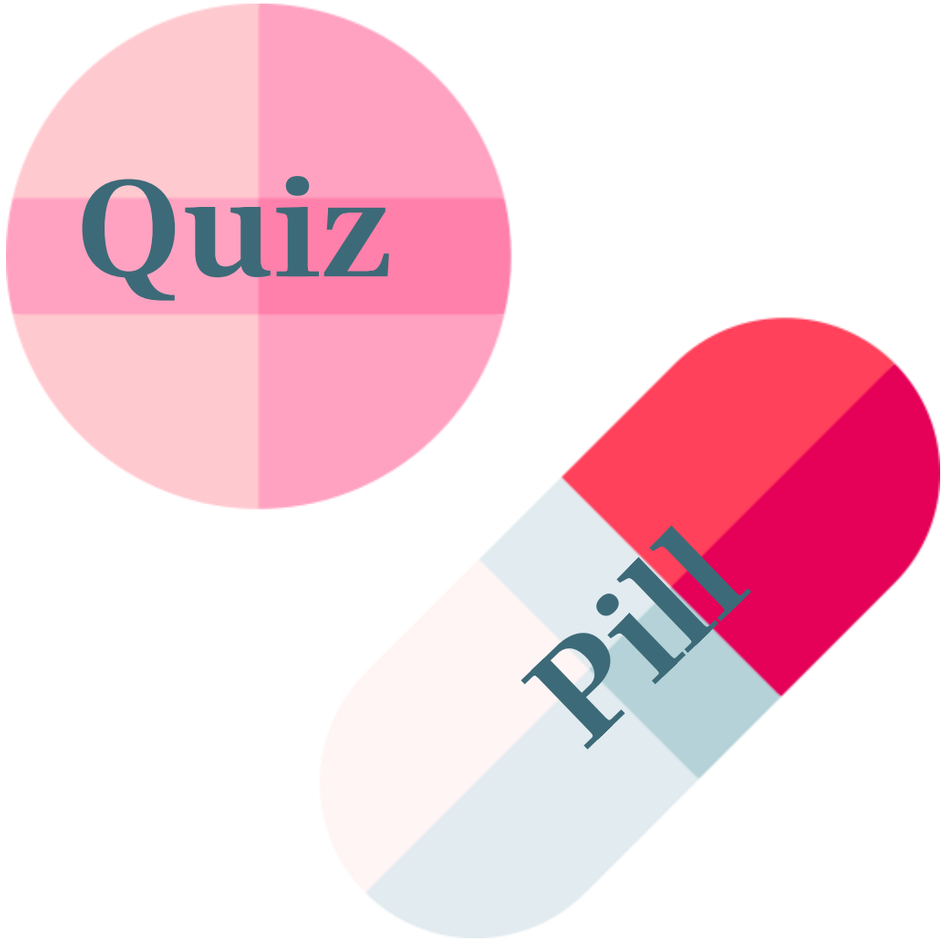
The doctor said he doesn't really care about this slide but study it for your USMLE=)

4)Hypersensitivity: with streptokinase & anistreplase (which includes streptokinase in its composition): streptokinase is purified from culture broths of streptococci→ it is a foreign body & is, thus, antigenic.

- Most people have had a streptococcal infection→they may have circulating antibodies against streptokinase→ the streptokinase- antibody reaction can cause fever, hypersensitivity &/or failure of therapy (because the streptokinase molecules complexed with the antibody are pharmacologically inactive).

- Urokinase is nonantigenic because it exists normally in human urine→ it is used in patients hypersensitive to streptokinase.

Pharmacology Quiz 3B



For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	According to the note 6 slide 7 and other resources, some changes were made in the slides : 3 4 Small note is added slide 8 point 3 The quiz is fixed	Reteplase is more fibrin-specific than Alteplase.	Reteplase is the least fibrin-specific drug among the mentioned tPA class drugs.
V1 → V2			