MED441
KING SAUD UNIVERSITY

Revised & Reviewed by: Abdulaziz & Bahammam Faye Wael Sendi

11.Thrombolytic drugs

Pharmacology
TEAM 441

Objectives:

- To know mechanism of action of thrombolytic therapy.
- To differentiate between different types of thrombolytic drugs.
- To describe indications, side effects and contraindications of thrombolytic drugs.
- To recognize the mechanisms, uses and side effects of antiplasmins.

HELPFUL VIDEO:

Thrombolytics

Editing file

Color index:
Important
In male's slides only
In female's slides only
Extra information
Doctors notes

This was added by the female's doctor, we will not be asked on it, it's only for better understanding

Anticoagulants	Antiplatelet drugs	Fibrinolytic/ Thrombolytic drugs (Our lecture)
Prevent thrombus formation and extension by inhibiting clotting factors .	Reduce risk of clot formation by inhibiting platelet functions	Dissolve already formed thrombi "Called fibrinolytics because they work on fibrin, which makes the clot stable"
Ex: heparin, low molecular weight heparin,coumarins/warfarin	Ex: Aspirin & ticlopidine	Ex: Streptokinase
Used for preventing the formation of blood clots (Prophylaxis)		Management of already formed blood clot (Emergency) "never used in prophylaxis"

"Thrombolytics are drugs that will breakdown a clot which is already formed, while anticoagulants prevent the formation of new clots"

Thrombolytic agents:

Definition Thrombolytics (Fibrinolytics) are drugs used to lyse **already formed** blood clots in clinical settings where ischemia may be fatal.

Goal of use The goal of thrombolytic therapy is rapid **restoration of blood flow** in an occluded vessel by accelerating proteolysis of the already formed thrombus.

Part of Thrombolytic therapy is one part of an overall antithrombotic plan that frequently includes anticoagulants, antiplatelet agents and mechanical approaches to rapidly restore flow and prevent re-occlusion.

Indications of Thrombolytics: "All conditions related to clot formation"

1. **Acute myocardial infarction (ST elevation, STEMI)**
2. **Peripheral artery occlusion**
3. **Pulmonary embolism**
4. **Acute ischemic stroke** Not hemorrhagic stroke
5. **Deep venous thrombosis**

Rationale for Use of Thrombolytic Drugs in AMI:

"AMI = Acute Myocardial Infarction"

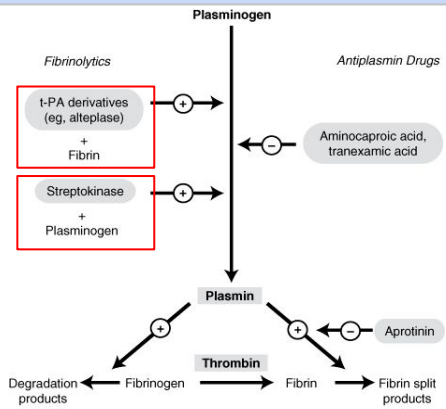
1. Improvement of ventricular function; reduction of the incidence of congestive heart failure and the reduction of mortality following AMI.

2. Thrombolytic drugs need to be given **immediately** to the patient after diagnosis of MI, delay in administration will be of no value.

Mechanism Of Action:

They have a common MOA by stimulating **plasminogen activation** via converting plasminogen* (proenzyme) to plasmin (active enzyme) → lysis of the insoluble fibrin clot into soluble derivatives. "In other word, enhancing plasmin activation, breaking down fibrin and restoring blood supply to blocked vessels"

*"gen means inactive"



What is plasmin?

Plasmin is a **nonspecific** protease capable of breaking down :

- **Fibrin**
- Other circulating proteins, including **fibrinogen**, **factor V**, and **factor VIII**.

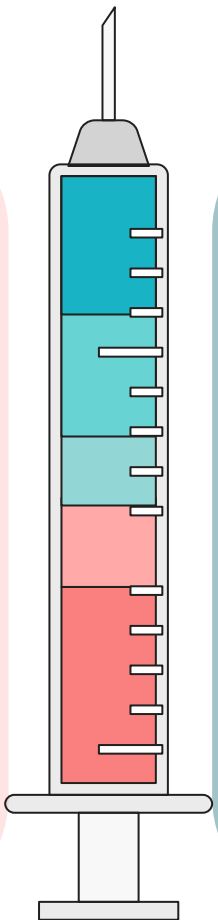
Types of thrombolytic drugs

Non-Fibrin specific agents

Activate both **plasminogen bound to clot surface and circulating plasminogen** in blood leading to extensive systemic plasminogen activation, with degradation of several plasma proteins including fibrinogen, factor V, and factor VIII.

-Binds equally to circulating and non-circulating plasminogen. "Less selective action"
-Produces breakdown of clot (local fibrinolysis) and circulating plasminogen and other plasma proteins thus cause an unwanted (systemic fibrinolysis) leading to bleeding.

-(**USA**): "USA is a big country → non-selective"
- **U**rokinase.
- **S**treptokinase.
- **A**nistreplase.



Fibrin specific agents

Fibrin specific plasminogen activators activate mainly **plasminogen bound to clot surface** and have less effect on circulating plasminogen.

-They are **tissue plasminogen activators.**
- Selective in action (clot or fibrin specific).
- Binds preferentially to plasminogen at the fibrin surface (non-circulating) rather than circulating plasminogen in blood. "More selective"
- Risk of bleeding is less than non specific agents.
- Activity is enhanced upon binding to fibrin.

-(**ART**):"A-R-T from shortest to longest duration of action"
- **A**lteplase
- **R**eteplase.
- **T**enecteplase

Non fibrin specific thrombolytic drugs

	Streptokinase (SK)	Anistreplase (APSAC)	Urokinase
M.O.A	- Is a bacterial protein produced by B-hemolytic streptococci. - It acts **indirectly** "it has to be combined first" by forming plasminogen-streptokinase complex **"activator complex"** which converts inactive plasminogen into active plasmin. - Can degrade fibrin clots as well as fibrinogen and other plasma proteins "Streptokinase is the only indirect acting thrombolytic".	Anisoylated Plasminogen Streptokinase Activator Complex(APSAC) is an acylated plasminogen combined with streptokinase. - It is a **prodrug**, de-acylated in circulation into the active plasminogen-streptokinase complex. Instead of giving streptokinase, we could directly give the active complex: plasminogen+streptokinase. The difference is that APSAC is a prodrug with an anisoyl group to block it's active site & prevent nonspecific degradation & hemorrhage. Although it's still not considered a selective drug,it is more selective than streptokinase & causes less side effects.	- Human enzyme synthesized by the kidney - Obtained from either urine or cultures of human embryonic kidney cells. - Is a direct plasminogen activator. "No formed complex"
T 1/2	**Less than 20 minutes**	**70-120 minutes**	**12-20 minutes.**
Administration	given as **intravenous infusion** (250,000 U then 100,000 U/h for 24-72 h).	Given as a **bolus I.V.** injection (30 U over 3 - 5 min.).	Given by **intravenous infusion** (300,000U over 10 min then 300,000U/h for 12h).
Advantages	- Least expensive. - Used for venous and arterial thrombosis.	- Longer duration of action than streptokinase. - More thrombolytic activity. - Greater clot selectivity. "Compared to streptokinase"	- Used for the lyses of acute massive pulmonary emboli - **No anaphylaxis** (not antigenic). "Because it is a human protein"
Side effects	1- **Antigenicity**: high-titer antibodies develop 1 to 2 weeks after use, precluding retreatment until the titer declines."because of its bacterial proteins, the body will develop antibodies against the drug" 2- **Allergic reaction**: like rashes, fever, hypotension"due to antigenicity" 3- **Bleeding** due to activation of circulating plasminogen (systemic fibrinolysis). 4- Not fibrin specific.	Similar but less than streptokinase alone in: - Antigenicity. - Allergic reactions. - Minimal fibrin specificity -Systemic lysis -**But** more expensive than streptokinase	- Minimal fibrin specificity - Systemic lysis (acts upon fibrin-bound and circulating plasminogen). - Expensive (its use is now limited).
Precautions	Not used in patients with: - Recent streptococcal infections. - Previous administration of the drug "because the antibodies against streptokinase are still in the circulation->patient won't respond to the drug (resistance)" - These patients may develop fever, allergic reactions and resistance upon treatment with streptokinase due to **antistreptococcal antibodies**.		

Fibrin specific thrombolytic drugs
Tissue Plasminogen Activators (t-PAs)

	Alteplase	**Reteplase**	**Tenecteplase**
M.O.A	- All are recombinant human tissue plasminogen activators (t–PA). - Prepared by recombinant DNA technology. Directly act by: - They activate **fibrin-bound plasminogen** rather than free plasminogen in blood. - Their action is **enhanced by the presence of fibrin.** - They bind to fibrin in a thrombus and convert the entrapped plasminogen to plasmin followed by activated local fibrinolysis with **limited systemic fibrinolysis**. "Only act on the site of the blood clot"		
Advantages "Opposite to streptokinase"	1. Fibrin-specific drugs (clot specific). 2. Limited systemic fibrinolysis. 3. Reduced risk of bleeding 4. Not-antigenic (can be used in patients with recent streptococcal infections or antistreptococcal antibodies).		
T 1/2	has very short half life (**5 min**)	longer duration than alteplase (**15 min**)	has half life of more than **30 min**
Administration	is usually administered as an **intravenous bolus followed by an infusion.** (60 mg i.v. bolus + 40 mg infusion over 2 h).	Given as **two I.V. bolus** injections of 10 U each	It can be administered as a **single IV bolus.**
Specificity	--	**Has enhanced fibrin specificity**	It is **more fibrin-specific & longer duration** than alteplase.
Uses	**-In ST-elevation myocardial infarction (STEMI)** **-Pulmonary embolism.**		**It is only approved for use in acute Myocardial infarction.** **"It is still a new drug"**

Contraindications to thrombolytics "All bleeding conditions"

Absolute contraindications:

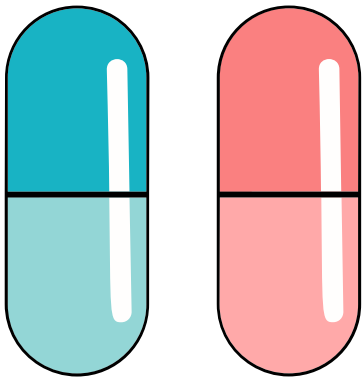
1- Active internal bleeding.

2- Cerebrovascular disease.

3- Major surgery within two weeks.

4- Recent intracranial trauma or neoplasm.

5- Cerebral hemorrhagic stroke.



Relative contraindications:

"Relative contraindications: could still be relatively used but not prefered"

1- Active peptic ulcer.

2- Severe uncontrolled hypertension.

3- Pregnancy or one week postpartum.

4- Oral anticoagulant therapy.

Female slides

Fibrinolytic Inhibitors "Used mainly in cases of thrombolytic overdose to prevent hemorrhage"

Fibrinolytic inhibitors (Antiplasmins) inhibit plasminogen activation and thus inhibit fibrinolysis and **promote clot stabilization.**

	Aminocaproic Acid & Tranexamic acid	Aprotinin
Administration	**Orally**	**Orally or I.V.**
M.O.A	Acts by competitive inhibition of plasminogen activation	It inhibits fibrinolysis by blocking the action of plasmin **(plasmin antagonist)**
Uses	- Fibrinolytic therapy induced bleeding (antidote). - Post surgical bleeding. - Post delivery. - Adjuvant therapy in hemophilia. - These drugs work like antidotes for fibrinolytic drugs. Similar to Protamine (antidote of anticoagulant, heparin) or Vitamin K (antidote of the oral anticoagulant, warfarin) Bleeding caused by? Warfarin(anticoagulant) : use vitamin K Heparin(anticoagulant) : use protamine Thrombolytics (fibrinolytic therapy) OR hemophilia (inherited) : use fibrinolytic inhibitors ex: aprotinin,aminocaproic acid, & tranexamic acid.	

SAQs:

Q1: What is the mechanism of action of thrombolytics?

Q2: What is the mechanism of action of Aprotinin ?

Q3: List 2 ADRs of Streptokinase?

Click here!

SUMMARY

A1: Converting plasminogen to plasmin leading to lysis of the insoluble fibrin clot into soluble derivatives.

A2: Inhibits fibrinolysis by blocking the action of plasmin (plasmin antagonist).

A3: 1-Bleeding. 2-Allergic reaction.

Test yourself

From our amazing Qbank team

Good luck!

Pharmacology
TEAM 441

Team leaders

Alanoud Alhaider **Faisal Alhussaini**

Subleader

Leen Alhadlaq

NOTE TAKER

Arwa Almobeirek

TEAM MEMBERS

Ayah Sayed
Dania Alhudaithi
Ghada Alharbi
Ghadah Fahad
Joud Alangari
Jumana Alqahtani
Norah Alqazlan
Nourah Alkhudiri
Noyer Awad
Raaoum Jabor
Rahaf Alrayes
Rand Aldajany
Reema Alrashedi
Refal Manhi
Sarah Alotaibi
Shahad Almuqbil
Abdullah Alghamdi
Abdullah Alyamani
Ahmed Khoja
Alwaleed Bin Shaya
Bassam Alhubaysh
Mansour Aldhalaan
Meshal Alqahtani
Talal Alanazy

Contact us:
pharmateam441@gmail.com

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