MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

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Thrombolytic drugs

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Green : Dr's notes
- Grey: Extra information, explanation

OBJECTIVES:

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

Editing File

thrombolytic agents

Definition

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

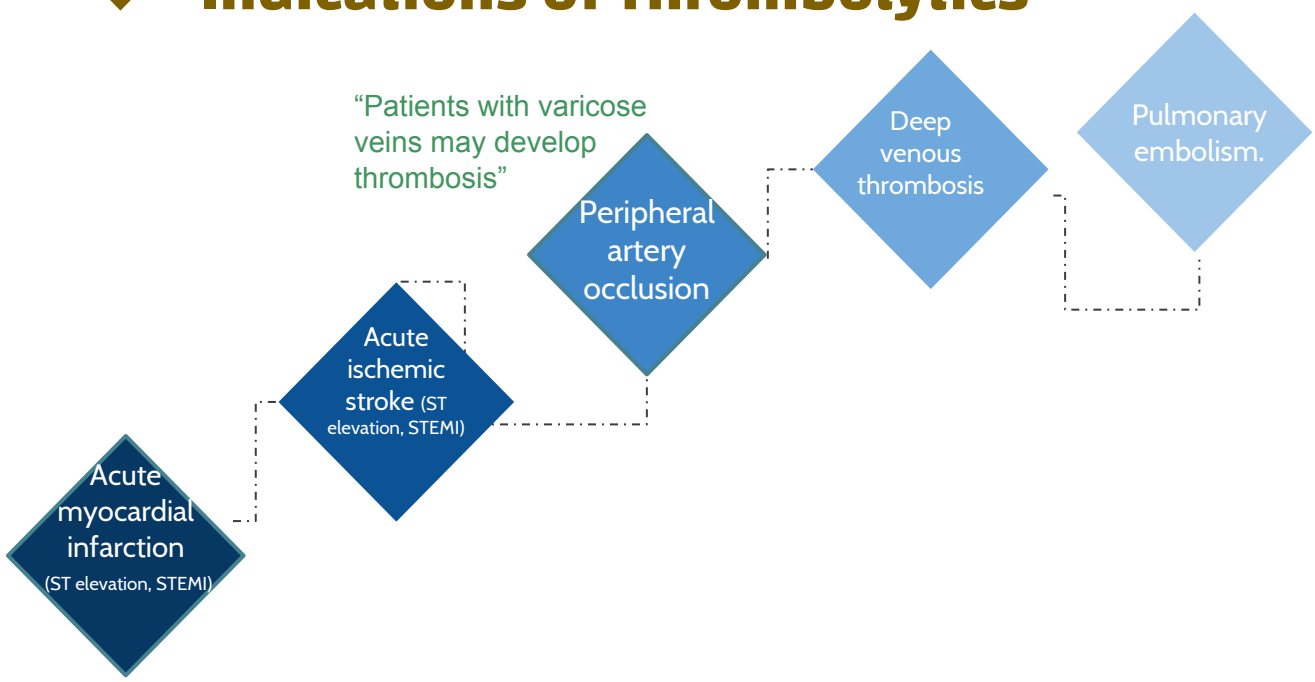
goal of use

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

considered as

Thrombolytic therapy is one part of an overall antithrombotic plan that frequently includes **anticoagulants** (These are usually used as prophylaxis after developing a thrombus and treating the patient with thrombolytic agents), **antiplatelet agents** and mechanical approaches to rapidly restore flow and prevent re-occlusion.

❖ Indications of Thrombolytics

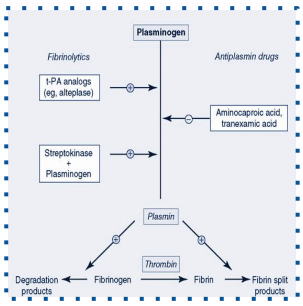


❖ Rational for Use of Thrombolytic Drugs in AMI:

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



Plasminogen —> plasmin —> lysis of the fibrin

They have common MOA by stimulating plasminogen"gen means inactive"

activation via converting plasminogen (proenzyme) to plasmin (active enzyme) → lysis of the insoluble fibrin clot into soluble derivatives.

Plasmin is a nonspecific protease capable of breaking down fibrin and other circulating proteins, including fibrinogen, factor V, and factor VIII.

Q: what will be the mechanism
By activating plasminogen into plasmin ---> Breaking down of the clot

Types of thrombolytic drugs

Both of them there will be bleeding but in non-specific higher than in specific

Non-Fibrin specific agent

- It binds equally to circulating and non-circulating plasminogen.
- produces breakdown of clot (local fibrinolysis) & circulating plasminogen & other plasma proteins thus causes an unwanted (systemic fibrinolysis) → **leads to bleeding**.
- E.g: (USA) :
  - Urokinase.
  - Streptokinase.
  - Anistreplase

Fibrin specific agent

- They are tissue plasminogen activators they act as tPA (human factor).
- & selective in action (clot or fibrin specific).
- they binds preferentially to plasminogen at the fibrin surface (non-circulating rather than circulating plasminogen in blood.
- Risk of bleeding is **less than** non specific agents.
- Activity is enhanced upon binding to fibrin.
- E.g: (ART):
  - Alteplase.
  - Reteplase.
  - Tenecteplase.

ART is according to duration of action A is the shortest while T is the longest

Non-Fibrin Specific Agents

Drugs	Streptokinase (SK)	Anistreplase (APSAC)	Urokinase
M.O.A	- It is a bacteria protein produced by B-hemolytic streptococci. - acts indirectly"the only drug" 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.	- **APSAC:** (Anisoylated Plasminogen Streptokinase Activator Complex) is an acylated plasminogen combined with streptokinase. - It is **prodrug,** de-acylated in circulation into the active plasminogen-streptokinase complex. - So it act directly.	- It is human enzyme synthesized by the kidney. - Obtained from either urine or cultures of human embryonic kidney cells. - it is a **direct** plasminogen activator.
T 1/2	**less than 20 minutes**	**70-120 minutes.**	**12-20 minutes.**
Administration	given as I.V. **infusion.**	given as **bolus** I.V. injection.	given by I.V. **infusion.**
Advantage	- It is the least expensive. - used for **venous** or **arterial** thrombosis.	- Longer duration of action than streptokinase - More thrombolytic activity. - Greater clot selectivity.	- Used for the lyses of **acute massive pulmonary emboli.** - No anaphylaxis****.
Side effects/ disadvantages	1- **Antigenicity*:** high titer antibodies developed 1 to 2 weeks after use, precluding retreatment until the titer declines. 2- **Allergic reaction:** like rashes, fever, hypotension "due to histamine". 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. **more expensive than streptokinase.**	- Minimal fibrin specificity. - Systemic lysis"high rating of bleeding"(acts upon fibrin-bound & circulating plasminogen). - Expensive (its used is now limited). Because it highly directly working drug so u expect more blinding
Precautions	Not used in patient with: 1- Recent streptococcal** infections, 2- Previous administration of the drug. these patients may develop fever, allergic reactions and resistance upon treatment with streptokinase due to antistreptococcal antibodies.	*Bacterial protein > foreign protein so it has antigenicity = it can produce antibodies and hypersensitivity, so histamine will release and the effect of autacoids will appear , to treat the patient we give corticosteroid **Patient with pharyngitis or streptococcal infection and Ab high in the body so when we give drug will be considered as antigen and will be destructed by Ab and will not be effective - ***Plasminogen is a human enzyme, and Streptokinase is a foreign protein, so when u give it as a complex the Antigenicity & Allergic reaction would be less. ****Urokinase is obtained from urine or human kidney cell, so there is NO allergic reaction or antigenicity.	

Fibrin Specific Agents

Tissue Plasminogen Activators (t - PA)

mnemonic:
T= time factor= long acting

Drugs	Alteplase	Reteplase	Tenecteplase
M.O.A	-Modified recombinant human t-PA Prepared By Recombinant Technology -**Direct action**: They activate **fibrin-bound plasminogen** rather than free plasminogen in blood. -Their action is **enhanced by the presence of fibrin**. -It binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin followed by activated local fibrinolysis with **limited systemic fibrinolysis.**		
Advantages	1. **Fibrin-specific drugs (clot specific).** 2. **Limited systemic fibrinolysis.** 3. **Reduced risk of bleeding** 4. **Not -antigenic (Can be used in patients with antistreptococcal antibodies).**		
T 1/2	**5 Min (short)**	**15 Min. (longer)**	**30 Min (the longest)**
Specificity	-	**Has Enhanced Fibrin Specificity**	**It Is More Fibrin specific.**
Administration	**i.v bolus followed by an infusion.**	**Two I.V. Bolus Injections**	**Single IV Bolus**
uses	**In ST-elevation myocardial infarction (STEMI) Pulmonary embolism**		**Only with approved for acute myocardial infarction (AMI)**

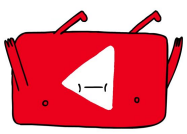
Contraindications To Thrombolytics

Absolute:

1. Active internal bleeding
2. Cerebral hemorrhagic stroke
3. cerebrovascular disease
4. Major surgery within two weeks
5. Recent intracranial trauma or neoplasm

Relative:

1. Active peptic ulcer
2. Severe uncontrolled hypertension
3. Pregnancy or within one week postpartum



a helpful video for the lecture by sketchyPharma

Fibrinolytic Inhibitors (Antiplasmin)

Drugs that inhibit plasminogen activation and thus inhibit fibrinolysis and promote clot stabilization.

Drug	Aminocaproic Acid + tranexamic acid	Aprotinin (More specific,effective.)
M.O.A	acts by competitive inhibition of plasminogen activation	It inhibits fibrinolysis by blocking the action of plasmin (plasmin antagonist)
administration	orally	orally or i.v
Uses	• Fibrinolytic therapy-induced bleeding (antidote) • Post-surgical bleeding • Adjuvant therapy in hemophilia • These drugs work like antidotes for fibrinolytic drugs. Similar to Protamine (Antidote of the anticoagulant, heparin) or Vitamin K (Antidote of the oral anticoagulant warfarin) Antidote= work against the drug	

Summary

Non-Specific Thrombolytic (systemic circulation) USA			
Drug	Streptokinase	Anistreplase	Urokinase
Mechanism	Activation of Streptokinase complex	Already made complex (prodrug)	Direct activator
T1/2	20 mins	70-120 mins	12-20mins
ADRs	-	Expensive	
	Antigenicity		-
	Allergic reaction		-
	Systemic lysis (bleeding)		
	Not fibrin specific	Minimal fibrin selectivity	
Indications	· Arterial thrombus · Venous thrombus	-	· Pulmonary thrombus
Contraindications	· Infections · Previous use	-	-

Specific Thrombolytic (Fibrin or clot-specific) ART			
Drug	Alteplase	Reteplase	Tenecteplase
Mechanism	They activate fibrin-bound plasminogen		
Advantage	· Less risk of bleeding · Limited lysis · Not antigenic		
T1/2	5 mins	15 mins	30 mins
Indications	· STEMI · Pulmonary E.	· STEMI · Pulmonary E.	· AMI
Contraindications	· Activate internal bleeding · Cerebral hemorrhage · Cerebrovascular disease · Surgery · Peptic ulcer · Hypertension		

Fibrinolytic inhibitors: prevent bleeding		
Drug	Aminocaproic Acid Tranexamic acid	Aprotinin
Mechanism	Competitive inhibition	Antagonism
Indications	· Hemophilia · Post-surgical bleeding · Fibrinolytic induced bleeding (antidote)such as: - Protamine (heparin antidote) - Vitamin K (warfarin antidote)	

QUIZ

MCQ

Questions 1–3:
A 55-year-old lawyer is brought to the emergency department 2 h after the onset of severe chest pain during a stressful meeting. He has a history of poorly controlled mild hypertension and elevated blood cholesterol but does not smoke. ECG changes (ST elevation) and cardiac enzymes confirm the diagnosis of myocardial infarction. The decision is made to attempt to open his occluded artery.

1- Which of the following drugs accelerates the conversion of plasminogen to plasmin?

A. Warfarin. B. Heparin C. Argatroban D. Reteplase

2- If a fibrinolytic drug is used for treatment of this man's acute myocardial infarction, which of the following adverse drug effects is most likely to occur?

A. Acute renal failure B. Development of antiplatelet antibodies
C. Encephalitis secondary to liver dysfunction D. Hemorrhagic stroke

3- What are other uses of this drug ?

A. Heart failure B. Pulmonary embolism C. Atherosclerosis D. Hypertension

4- Which is considered "fibrin selective" because it rapidly activates plasminogen that is bound to fibrin?

A. Alteplase. B. Fondaparinux. C. Streptokinase. D. Urokinase.

1-D 2-D 3-B 4-A

SAQ

A 67-year-old woman presents with pain in her left thigh muscle.Duplex ultrasonography indicates the presence of deep vein thrombosis (DVT) in the affected limb. The decision was made to treat this woman with reteplase.

1- What is the mechanism of action of this drug ?
They activate fibrin-bound plasminogen rather than free plasminogen in blood.

2- What are the clinical uses of this drug?
1-In ST-elevation myocardial infarction (STEMI)
2-Pulmonary embolism.

3- What is the preferred route?
I.V. bolus injections

pharmacology

Team 438

GOOD LUCK

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Share with us your ideas !