



King Saud University
College of Medicine
1st Year, 4th Block

Thrombolytic therapy

13

The last lecture ☺



CARDIOVASCULAR BLOCK

Objectives :

- 1 **To know mechanism of action of thrombolytic therapy.**
- 2 **To differentiate between different types of thrombolytic drugs.**
- 3 **To describe Indications, side effects and contraindications of thrombolytic drugs.**
- 4 **To recognize the mechanisms, uses and side effects of antiplasmins.**



Thrombolytics

Thrombolytic agents are used to lyse already formed blood clots in clinical settings where ischemia may be fatal.

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

Thrombolytic therapy

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

- 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 reocclusion.

Mechanism of Action

They have common mechanism of action by converting the proenzyme (plasminogen) to active enzyme (plasmin) → lysis of fibrin clot.

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

plasmin, degrades the insoluble fibrin clot matrix into soluble derivatives.

Types of thrombolytic drugs

Non-fibrin specific

Streptokinase
Anistreplase
Urokinase

(USA)

- binds equally to **circulating** and **non-circulating** plasminogen.
- produces breakdown of clot (**fibrinolysis**) and circulating fibrinogen (**fibrinogenolysis**), cause systemic fibrinolytic state leading to **bleeding**.
- degradation of several plasma proteins including **fibrinogen**, **factor V**, and **factor VIII**.

Fibrin specific

Alteplase
Retepase
Tenecteplase

(RAT)

- are tissue plasminogen activators
- selective in action (clot-specific fibrin).
- Activity is enhanced upon binding to fibrin.
- binds preferentially to plasminogen at the **fibrin surface (non-circulating)** rather than **circulating** plasminogen.
- risk of bleeding is less than non specific agents.

Indications of thrombolytics

- Acute myocardial infarction (ST elevation, STEMI).
- Acute ischemic stroke.
- Peripheral artery occlusion.
- Pulmonary embolism.
- Deep venous thrombosis.

Contraindications to Thrombolytics

- Active internal bleeding.
- Recent intracranial trauma or neoplasm.
- Cerebral hemorrhagic stroke.
- Cerebrovascular disease.
- Major surgery within two weeks.
- Active peptic ulcer.
- diabetic retinopathy.
- Pregnancy.

Streptokinase (SK)

Is a bacterial protein produced by B-hemolytic streptococci.

Action	<ul style="list-style-type: none">- It acts indirectly by forming plasminogen-streptokinase complex "activator complex" which converts other inactive plasminogen into active plasmin.- Plasmin degrades fibrin clots as well as fibrinogen and other plasma proteins (non-fibrin specific).
Uses	<ul style="list-style-type: none">- Half life less than 20 minutes- given as intravenous infusion (250,000U then 100,000U/h for 24-72 h).- used for venous or arterial thrombosis- Life threatening pulmonary embolism
Advantage	It is the least expensive
Side effects	<ul style="list-style-type: none">- Bleeding due to activation of circulating plasminogen (systemic fibrinolysis)- Antigenicity and high-titer antibodies develop 1 to 2 weeks after use, retreatment until the titer declines- Allergic reaction: like rashes, fever, hypotension- Prior exposure to the streptokinase or infection can cause sever allergic reaction
Precautions "Not used in patients with"	<ul style="list-style-type: none">- Recent streptococcal infections or pharyngits- Previous administration of the drug- These patients may develop fever, allergic reactions and resistance upon treatment with streptokinase due to antistreptococcal antibodies

	<h2 style="text-align: center;">Anistreplase (APSAC)</h2> <p style="text-align: center;">(Anisoylated Plasminogen Streptokinase Activator Complex)</p>	<h2 style="text-align: center;">Urokinase</h2> <p style="text-align: center;">(Human enzyme synthesized by the kidney)</p>
<p style="text-align: center;">Action</p>	<ul style="list-style-type: none"> -(APSAC) acylated plasminogen combined with streptokinase. -It is a prodrug, de-acylated in circulation into the active plasminogen-streptokinase complex. -Half life is <u>70-120 min</u> 	<ul style="list-style-type: none"> -obtained from either urine or cultures of human embryonic kidney cells. -acts directly to convert plasminogen to active plasmin. -Given by IV infusion. -Half life: 12-20 min. -Used for the lyses of acute massive pulmonary emboli
<p style="text-align: center;">Advantage</p>	<ul style="list-style-type: none"> - Given as a bolus I.V. injection - Longer duration of action than SK. - More thrombolytic activity than SK. - Greater clot selectivity than SK. 	<p>No anaphylaxis (not antigenic).</p>
<p style="text-align: center;">Disadvantages</p>	<p>Similar but but less than Streptokinase alone in:</p> <ul style="list-style-type: none"> -Antigenecity. -Allergic reactions -minimal fibrin specificity . -systemic lysis -but more expensive than SK 	<ul style="list-style-type: none"> -Minimal fibrin specificity. -systemic lysis (because it does not discriminate between fibrin-bound and circulating plasminogen) -Expensive.

Tissue Plasminogen Activators (t - PA):

All are recombinant tissue plasminogen activators (t –PA).

- Prepared by recombinant DNA technology Such as: Alteplase, Reteplase, and Tenecteplase (RAT)

* Mechanism of (t- PA):



Advantages of t-PA

Fibrin-specific drugs (clot specific).

Works At the site of thrombus

Limited systemic fibrinolysis.

Reduced risk of bleeding

T-PA produced by human endothelium so not antigenic
Can be used in patients with antistreptococcal antibodies

	Alteplase	Reteplase	Tenecteplase (TNK-tPA)
type	is a recombinant form of human tPA.	A variant of recombinant tPA	prepared by recombinant technology
Half life	has very short half life (~5 min)	It has longer duration than alteplase (15 min.)	It has half life of more than 30 min <u>longer duration</u> than alteplase.
Specificity		Has enhanced fibrin specificity	It is <u>more fibrin-specific</u> .
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.
ECG changes	-	In ST-elevation myocardial infarction (STEMI); improvement of ventricular function; reduction of the incidence of CHF and the reduction of mortality following AMI.	-
Uses	-	Pulmonary embolism.	It is only approved for use in acute myocardial infarction.

Fibrinolytic Inhibitors Antiplasmin

inhibit the activation of plasminogen and lead to inhibit fibrinolysis and these two things leading to promote the clot

1-Aminocaproic Acid & tranexamic acid :
acts by competitive inhibition of plasminogen activation. Given orally.

2-Aprotinin:
It inhibits fibrinolysis by blocking plasmin
Given orally + I.V bolus

Uses of Fibrinolytic Inhibitors:

- 1-Adjuvant therapy in hemophilia
- 2-Fibrinolytic therapy-induced bleeding (antidote).
- 3-Postsurgical bleeding

These drugs work like antidotes for fibrinolytic drugs.

- 1-protamine antidote to heparin
- 2-vit K antidote to warfarine

SUMMARY

Non-fibrin specific			Fibrin specific (**t-PA)		
Breakdown of clot (fibrinolysis) and circulating fibrinogen (fibrinogenolysis)			Breakdown of only clot –non circulating- (fibrinolysis)		
Streptokinase	Anistreplase	urokinase	Alteplase	Retepase	Tenecteplase
It's a bacterial protein, acts indirectly	It's acylated plasminogen combined with streptokinase, it's a prodrug	It's human enzyme synthesized, acts directly	It's a recombined form of human t-PA	It's a variant of recombinant t-PA	It's another genetically modified human t-PA, IT'S MORE FIBRIN-SEPCIFIC
Used Atrial and venous Life threatening pulmonary embolism	More active and more clot selective than streptokinase	Used in acute massive pulmonary embolism		Used in myocardial infarction and pulmonary embolism	Only approved to use in acute myocardial infarction
Side effects: Bleeding Antigenicity Allergic reaction	Side effects: Similar to streptokinase	Not antigenic	<u>These are drugs inhibit the plasminogen:</u> <ol style="list-style-type: none"> 1. Aminocaproic acid (competitive inhibition, orally) 2. Tranexamic acid (competitive inhibition, orally) 3. Aprotinin (blocking plasmin, orally or I.V) 		

MCQs

Q1 - Patient has arterial thrombosis , and he has streptococcal infections , which one of these drugs we should not give him ?

- A. Urokinase
- B. Streptokinase
- C. Anistreplase
- D. Alteplase

Q2 - Which one of these drugs are produced by B-hemolytic streptococcus ?

- A. Alteplase
- B. Urokinase
- C. Streptokinase
- D. Anistreplase

Q3 - Which one of the following enzymes synthase by kidney ?

- A. Urokinase
- B. Streptokinase
- C. Anistreplase
- D. Alteplase

Q4 - A patient came to KKUH with acute massive pulmonary emboli , which one of the following the doctor should give him ?

- A. Urokinase
- B. Streptokinase
- C. Anistreplase
- D. Tenecteplase

Q5 - A patient came to the emergency , after examination , the doctor diagnose him with acute myocardial infraction , which one of the following drugs should he takes ?

- A. Tenecteplase
- B. Streptokinase
- C. Anistreplase
- D. Reteplase

Q6 - Which one of these are used in Pulmonary embolism ?

- A. Alteplase - Tenecteplase
- B. Alteplase - Reteplase
- C. Reteplase – Tenecteplase
- D. Tenecteplase – urokinase

Q7 –which one of the following is plasmin antagonist ?

- A. Tenecteplase
- B. Aprotinin
- C. Anistreplase
- D. Reteplase

7-B

6-B

5-A

4-A

3-A

2-C

1-B



THIS WORK WAS DONE BY :

Contact us for any questions or
comments :



Pharma_433@yahoo.com



@pharma_433

Nada Dammas

Ahmed Aldakhil

Rawan AlBadai

Abdulaziz Almasoud

Ziyad Alajlan

Abdulrahman Alqahtani

Abdulmalek Alnujidi

Ahmed Alzoman

Faroq Abdulafattah

**We hope that we made this lecture easier for you
Good Luck !**