

PHARMACOLOGY

Thrombolytic therapy

❖ 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 anti-plasmins.

• Terminology:

IV injection is either :



Bolus : a single dose of a drug or other medicinal preparation given all at once.



Infusion : the slow injection of a substance into a vein or tissue.



PHARMACOLOGY

435

- Important.
- Extra notes.
- Mnemonic.

Thrombolytic agents (AKA: plasminogen activators):
drugs used to **lyse already formed blood clots** in clinical settings where this clot is obstructing blood flow and causing ischemia (which may be fatal).

Antithrombotic plan includes Thrombolytics, Anticoagulants, Antiplatelet agents and mechanical approaches.

The goal is to:

- 1. Rapidly restore flow by accelerating the proteolysis of thrombus.**
This is the goal for Thrombolytic therapy.
- 2. Prevent re-occlusion by the soluble degraded products.** This is achieved by the concomitant use of Anticoagulants & antiplatelets.

USES of antithrombotic plan:

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

Rational (aim) for use of thrombolytic drugs in AMI:

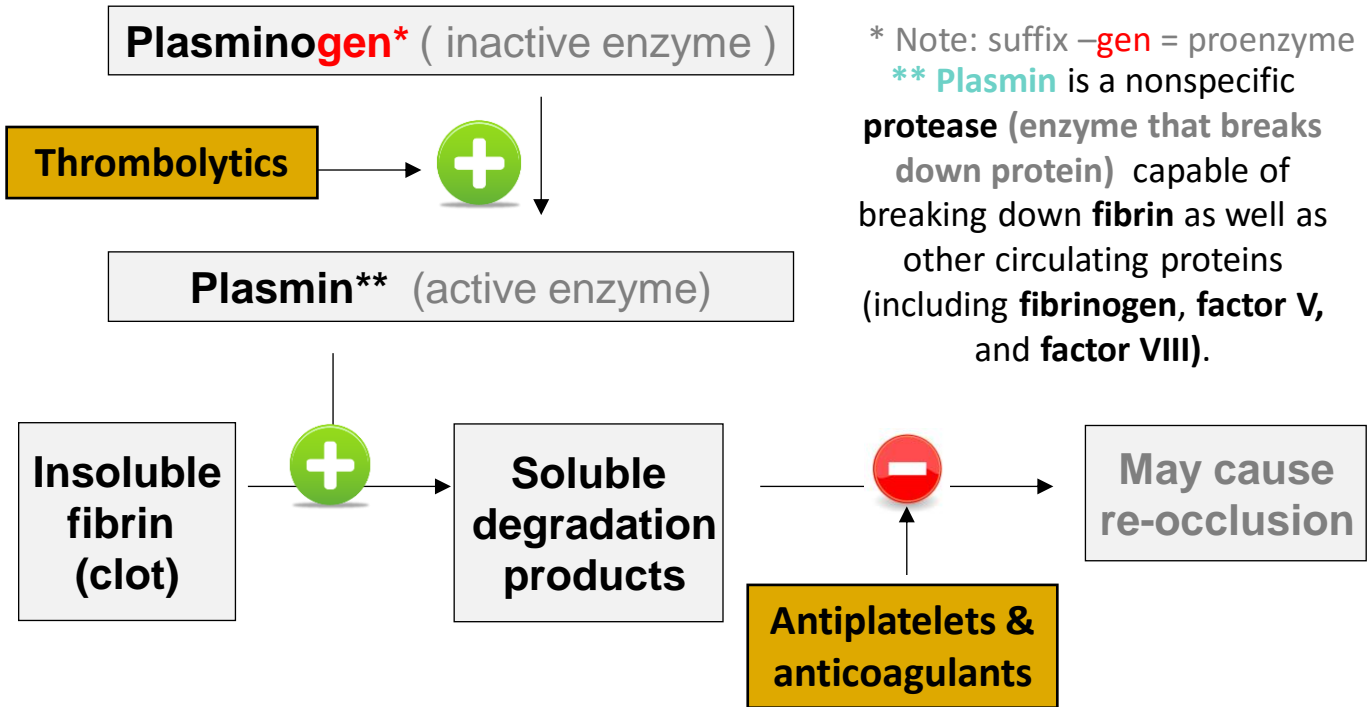
- 1) Improvement of ventricular function
- 2) Reduction of incidence of Congestive heart failure (CHF)
- 3) Reduction of mortality due to AMI

* **Thrombolytics** Need to be given **IMMEDIATELY** to the patient after diagnosis with MI. Delay in administration will be of no value in treatment, due to emergence of irreversible necrosis.

Plasminogen is a proenzyme that degrades plasma proteins, it is present in:

1. Clot surface, bound to fibrin in thrombus. If this plasminogen is activated, fibrin will be degraded, and thus clots blocking blood flow will be lysed. (desirable)
2. Blood circulation, helping in physiological blood clot (as in wound healing). Activation of this plasminogen will degrade circulating proteins including fibrinogen, factor V, and factor VIII, resulting in systemic fibrinolysis and thus bleeding. (undesirable)

Common Mechanism of Action of thrombolytic drugs



Thrombolytic drugs (plasminogen activators)

Types	Fibrin Specific AKA: Tissue plasminogen Activators (t-PA)	Non fibrin-specific
Action	They activate mainly plasminogen bound to clot surface (non-circulating plasminogen in tissue) and have less effect on circulating plasminogen. *Once they bind to fibrin, their activity is enhanced*	Activate both plasminogen bound to clot surface and circulating plasminogen in blood. “systemic plasminogen activation”
Risk of bleeding	Less, because of selectivity to fibrin (clot).	More , systemic plasminogen activation → systemic fibrinolysis → degradation of several plasma proteins (including fibrinogen, factor V, and factor VIII) → bleeding .
Examples	Alteplase – Reteplase – Tenecteplase (RAT)	Streptokinase – Anistreplase – Urokinase (USA)

Non- fibrin selective thrombolytics: Streptokinase (SK)

Streptokinase (SK)

Information	Strepto kinase is a Bacterial protein produce by B-hemolytic streptococci
Type	Non fibrin-specific (can degrade fibrin clots as well as fibrinogen and other plasma proteins)
Mechanism of action	Acts Indirectly by binding with plasminogen and forming plasminogen-streptokinase complex (activator complex) which converts inactive plasminogen into active plasmin.
T _{1/2}	Less than 20 minutes
administration	I.V infusion
Uses	Used for <u>Venous or arterial thrombosis</u> , as it is the cheapest among others.
Side effects	<ul style="list-style-type: none">• Antigenicity: since streptokinase is a bacterial protein (foreign protein), high-titer antibodies develop 1 to 2 weeks after use. Thus, retreatment by streptokinase should be precluded (prevented) until titer decline.• Allergic reaction (causing rashes, fever, hypotension)• Bleeding. Due to activation of circulating plasminogen (systemic fibrinolysis), since it is not fibrin specific.
Precaution (shouldn't be used in patients with...)	Recent streptococcal infection OR previous administration of the drug (within 6 months). If used in these Patients, allergic reaction and resistance (failure of therapy to drug) may develop due to anti streptococcal antibodies

Non- fibrin selective thrombolytics: Anistreplase & Urokinase

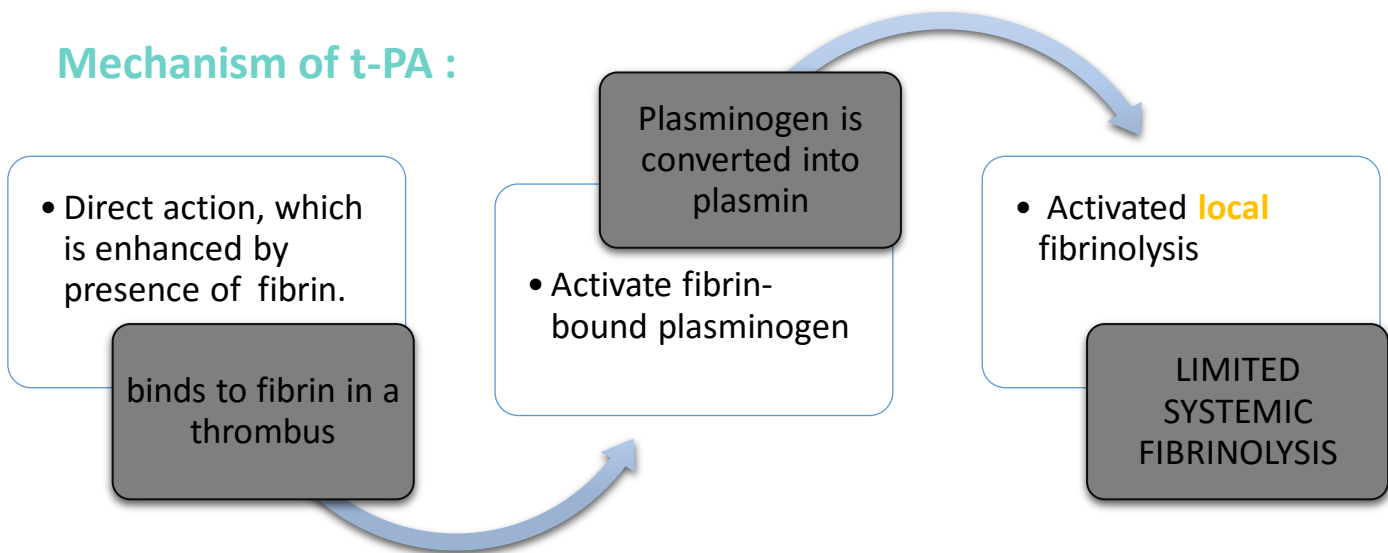
	Anistreplase (APSAC)	Urokinase
General Information	<p>Anisoylated Plasminogen-Streptokinase Activator Complex (APSAC) is an acylated plasminogen combined with streptokinase. It is a prodrug, de-acylated in circulation into the active (not anisoylated) plasminogen-streptokinase complex.</p>	<p>Human enzyme synthesized by the kidney. obtained from either urine or cultures of human embryonic kidney cells. Acts directly to convert plasminogen to active plasmin.</p>
Admin.	bolus I.V. injection	IV infusion.
T _{1/2}	70-120 min (longer)	12-20 min
Uses	-	-Used for the lyses of acute massive pulmonary emboli
Advantage	<p>In comparison with streptokinase (SK):</p> <ul style="list-style-type: none"> • Longer duration of action • More thrombolytic activity • Greater clot selectivity <ul style="list-style-type: none"> • less than SK alone in: <ul style="list-style-type: none"> -Antigenicity (plasminogen is a normal human protein, it reduces the Ag-Ab reaction of streptokinase when combined with it) -Allergic reactions -minimal fibrin specificity. -systemic lysis 	<p>No anaphylaxis (not antigenic since there is no foreign protein)</p>
Disadvantages	- more expensive than SK	- Very Expensive, which is why its use is now limited.

Tissue Plasminogen Activators (t - PA)

Fibrin-selective thrombolytics, commonly known as: Tissue Plasminogen Activators (t - PA)

- All are recombinant tissue plasminogen activators (t –PA), Prepared by recombinant DNA technology.
- Recombinant DNA technology: inserted DNA sequence of the desired protein (e.g. tPA) into bacteria (e.g. E.coli), which propagates and proliferate quickly to produce large amounts of the desired protein (e.g. tPA). Then finally purified and used as a drug.
- Include drugs as (RAT) :
 1. Alteplase
 2. Reteplase
 3. Tenecteplase

Mechanism of t-PA :



Advantages of t-PA :

- Fibrin-specific drugs (clot specific) → Limited systemic fibrinolysis → Reduced risk of bleeding.
- Not-antigenic : Can be used in patients with antistreptococcal antibodies (due to either recent infection or use of streptokinase).

Tissue Plasminogen Activators (t - PA):

	Alteplase	Retepase	Tenecteplase (TNK-TPA)
Type	A Recombinant Form Of Human tPA.	modified recombinant human t-PA Prepared By Recombinant Technology	
T _{1/2}	5 Min (short)	15 Min. (longer)	30 Min (the longest)
Specificity		Has Enhanced Fibrin Specificity	It Is More Fibrin-specific.
Administration	IV Bolus Followed By An Infusion.	Two I.V. Bolus Injections	Single IV Bolus.
Uses	<ul style="list-style-type: none"> ST-elevation Myocardial Infarction (STEMI) Pulmonary Embolism. 		only approved for Acute Myocardial Infarction (AMI)

Contraindications to thrombolytics:

In cases of bleeding or risk of bleeding (with use of thrombolytics).

Absolute contraindications include:

- Active internal bleeding
- Cerebral hemorrhagic stroke
- Recent intracranial trauma or neoplasm
- Major surgery within two weeks

Relative contraindications include:

- Active peptic ulcer
- Severe uncontrolled hypertension.

Antidotes

If a toxic dose of thrombolytics was given and resulted in bleeding, fibrinolytic inhibitors can be used to reverse their effects.

	Fibrinolytic Inhibitors (Antiplasmins) Inhibit plasminogen activation and thus inhibit fibrinolysis and promote clot stabilization.	
Drug	Aminocaproic Acid & tranexamic acid	Aprotinin
Mechanism	Competitive Inhibition of Plasminogen Activation	inhibits fibrinolysis by blocking the action of plasmin (Plasmin antagonist)
Admin.	Orally	Orally or IV
uses	<ul style="list-style-type: none"> • Adjuvant therapy in hemophilia • Postsurgical bleeding • Antidote for Fibrinolytic therapy-induced bleeding. • These drugs work like antidotes for fibrinolytic drugs. 	

Anticoagulants and antiplatelets are used to prevent re-occlusion by blood clot in antithrombotic therapy.

Anticoagulant	• Warfarin	• heparin
Administration	• oral anticoagulant	• Injection
Antidote	• Vitamin K	• Protamine

Antiplatelet	• E.g. Aspirin
Action	• decrease platelet aggregation and inhibit thrombus formation.

THANK YOU FOR CHECKING OUR WORK

435 PHARMACOLOGY TEAM

Quiz

عبدالرحمن السيارى
أحمد اليحيى
خالد الزهرانى
عبدالله الجنيدل
أحمد المصعبى
عبدالرحمن الزامل
عبدالرحمن الشمري
معاذ باعشن
عبدالعزيز الشعلان
محمد السحيباني
فارس المطيري
فوزان العتيبي
محمد ابونيان
عمر القحطاني
يوسف الصامل

شماء السعد
رهدف بن عبّاد
سارة الخليفة
ساره المطوع
فاطمة الدين
آية غانم
أسرار باطرفي
نوف عبدالكريم
وضحى العتيبي
ريما الحيدان

لولوه الصغير
شادن العمران
لمى الزامل
كوثر موسى
ديمه الراجحي
جواهر الحربي
دلال الحزيمي
رنيم الدبيخي
نورة الصومالي
منيرة السلولي

For any correction, suggestion or any useful information do not
hesitate to contact us : Pharmacology.med435@gmail.com



PHARMACOLOGY
435

