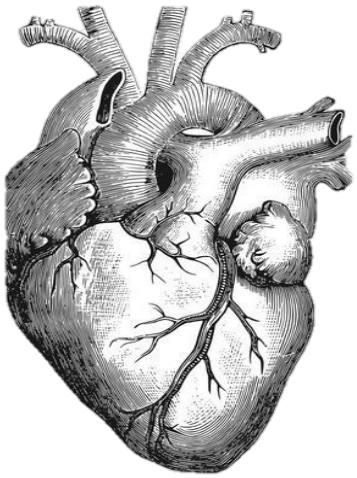
Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY



Thrombolytics

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.

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Thrombolytic Agents

What are thrombolytic agents?

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

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

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

used for the treatment of:

- **Acute myocardial infarction (ST elevation, STEMI).**
- **Acute ischemic stroke.**
- **Peripheral artery occlusion.**
- **Deep venous thrombosis.(most common indication, especially after surgery or after plane rides and long durations of immobilization in general)**
- **Pulmonary embolism.**

Thrombolytic Agents

Rational for Use of Thrombolytic Drugs in AMI

- **Improvement of ventricular function; reduction of the incidence of congestive heart failure and the reduction of mortality following AMI.**
- **Thrombolytic drugs need to be given immediately to the patient after diagnosis of MI, delay in administration will be of no value.**

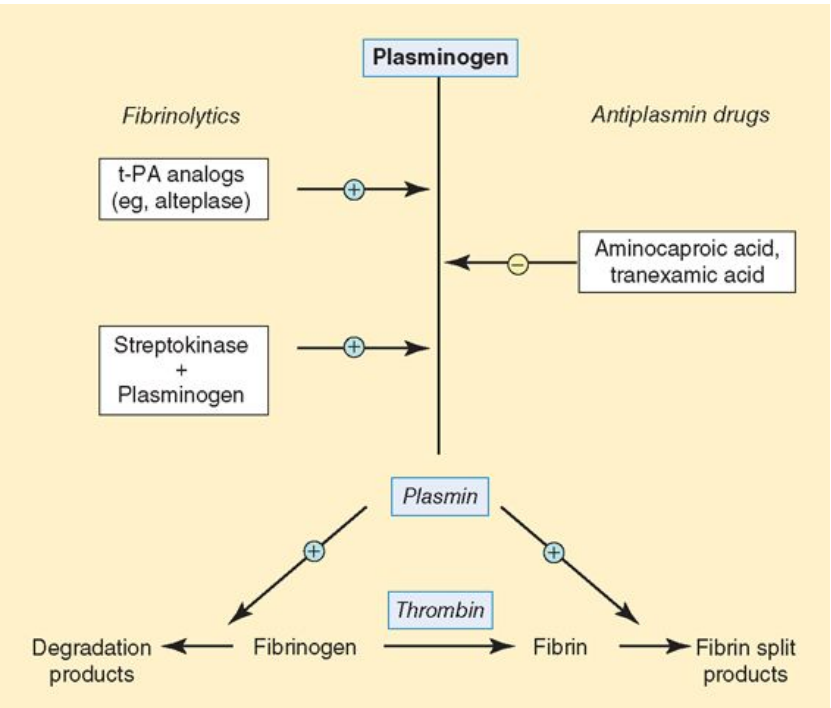
Mechanism of Action of Thrombolytic Drugs

They have common mechanism of action by stimulating plasminogen 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 as well as other circulating proteins, including fibrinogen, factor V, and factor VIII.

A helpful video

Special thanks to Norah Alharbi!



Types of Thrombolytics

Type of Drug	Non Fibrin-Specific Agent	Fibrin-Specific Agent
Action	1-binds equally to circulating and non-circulating plasminogen. 2-produces breakdown of clot (local fibrinolysis) and circulating plasminogen and other plasma proteins thus cause an unwanted (systemic fibrinolysis) leading to bleeding	1-tissue plaminogen activators 2-selective in action (clot or fibrin specific) 3-binds preferentially to plasminogen at the fibrin surface (non-circulating) rather than circulating plasminogen in blood. 4-Risk of bleeding is less than non specific agents 5-Activity is enhanced upon binding to fibrin
Example	–Streptokinase –Anistreplase –Urokinase (USA) Take note that all fibrin specific thrombolytics end with plase except ANIstrePLASE (he goes any place-non fibrin specific)	–Alteplase shortest duratiom of action –Reteplase –Tenecteplase longest duration of action (RAT)

Non-Fibrin Specific Agents

drugs	Streptokinase	Anistreplase	Urokinase
mechanism of action	-Is a bacterial protein pruduced by B-hemolytic streptococci -It acts indirectly (the only indrectly acting 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	-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 anislyated) plasminogen streptokinase complex.	-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.
T 1/2	<20 minutes	70-120 min (longer)	12-20 min
Administration	given as IV infusion	bolus I.V. injection	IV infusion.
Advantage	-used for venous or arterial thrombosis. -It is the least expensive.	In comparison with streptokinase (SK): -Longer duration of action -more thrombolytic activity -Greater clot selectivity	-Used for the lyses of acute massive pulmonary emboli -No anaphylaxis (not antigenic)
Disadvantage	**1**-Antigenicity: high-titer antibodies develop 1 to 2 weeks after use, precluding retreatment until the titer declines Why? Because of its foreign bacterial proteins, the body will develop antibodies against the drug. **2**-Allergic reaction: like rashes, fever,hypotension **3**-Bleeding due to activation of circulating plasminogen (systemic fibrinolysis). cause it is **4**-not fibrin specfic	-Similar to streptokinase but less severe. Why? Some of it is made of human so antigenicity is less causing less effect than streptokinase -more expensive than SK and more effective	-minimal fibrin specificity - expensive -Systemic lysis (acts upon fibrin-bound and circulating plasminogen).

Precaution: Streptokinase should not be used in patients with:
1-Recent streptococcal infection
2-Previous administration of drug
These patients may develop fever, allergic reactions, and resistance after treatment with streptokinase due to anti streptococcal antibodies

Fibrin Specific Agents (Tissue Plasminogen Activators (t - PA))

drugs	Alteplase	Reteplase	Tenecteplase
Action	-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	-Fibrin-specific drugs (clot specific). -Limited systemic fibrinolysis. -Reduced risk of bleeding -Not -antigenic (Can be used in patients with antistreptococcal antibodies).		
T 1/2	5 Min (short)	15 Min. (longer)	30 Min (the longest) -T for time
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 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

Fibrinolytic Inhibitors(Antiplasmin)

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

Drug	Aminocaproic Acid + tranexamic acid	Aprotinin
mechanism of action	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 of Fibrinolytic Inhibitors

1-Adjuvant therapy in hemophilia

2-Fibrinolytic therapy-induced bleeding (antidote).

3-Post-surgical bleeding

4-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)

Questions

MCQs:

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.

Questions

MCQs:

5. Which one of the following is a Anistreplase disadvantage ?
A. Given as a bolus I.V. injection
B. Long duration of action
C. Minimal fibrin specificity
D. Greater clot selectivity.

1-D 2-D 3-B 4-A 5-C

Questions

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 ?

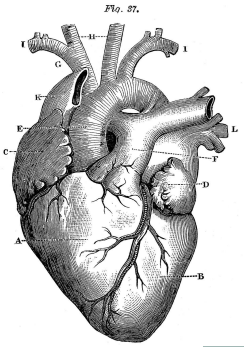
They activate fibrin-bound plasminogen rather than free plasminogen in blood.

2. What are the clinical uses of this drug?

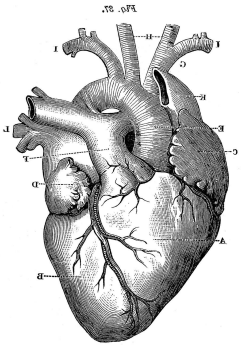
1-In ST-elevation myocardial infarction (STEMI)
2-Pulmonary embolism.

3. What is the preferred route?

I.V. bolus injections



"It is not hard, you just made it to the end!"



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References:

✓ Doctors' notes and slides

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