Thrombolytic Therapy

By

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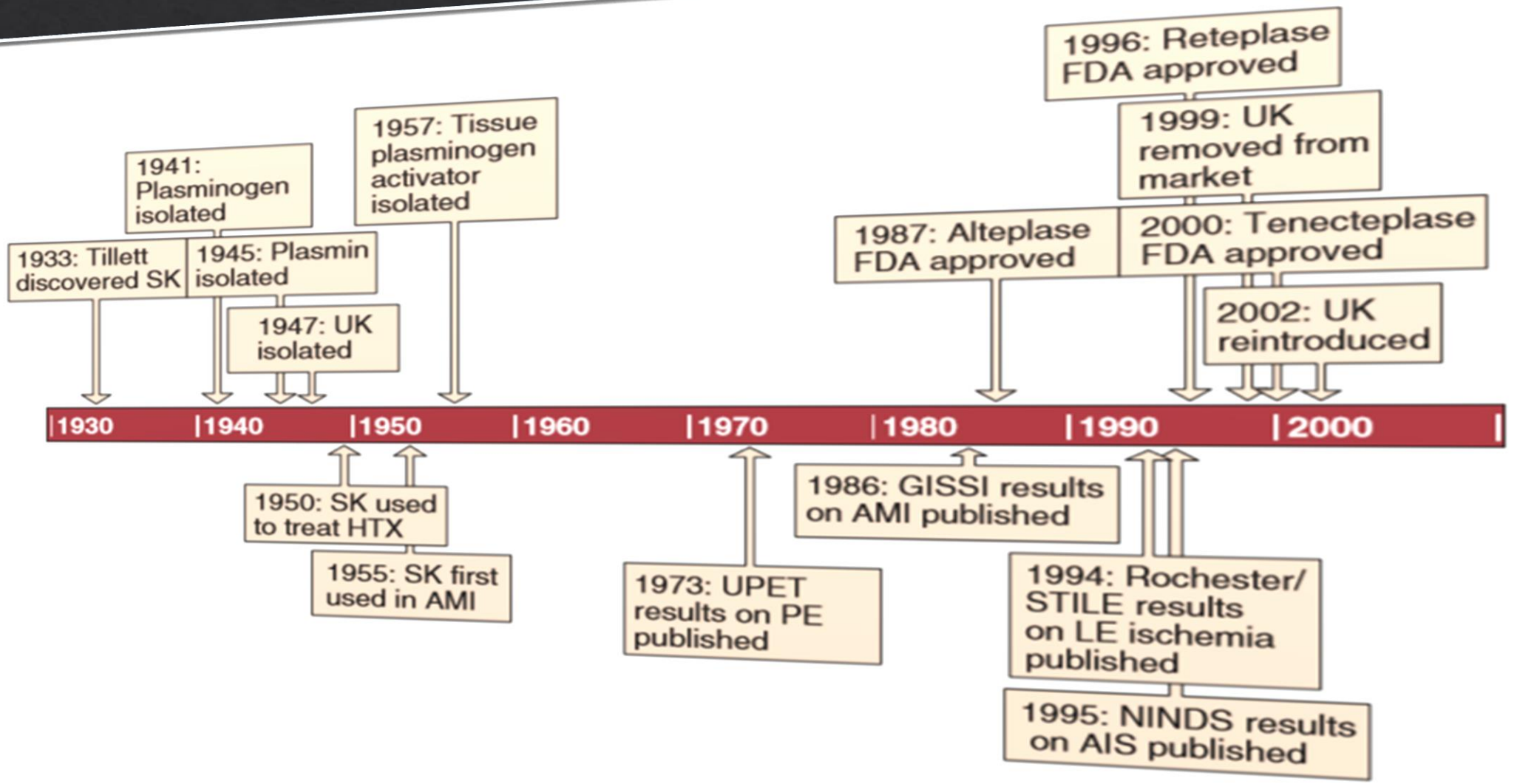
History

- Morgagni (1761) noted blood forms clots post-mortem, followed by reliquefication.
- Dastre (1893) coined term “fibrinolysis” describe disappearance of fibrin from dogs who repeatedly hemorrhaged .
- Morawitz (1906) noted post-mortem blood destroys fibrinogen and fibrin in normal blood. (inactive component of blood, controlled by a “regulator,” could be converted into a “fibrin-degrading agent)

- Milstone 1941 Inactive component (lytic factor)was first described by is now known as plasminogen.
- Tillett 1933 The discovery of the first fibrinolytic agent, SK, came by chance at Johns Hopkins University.
- Tillett and Sherry 1954 the first human intravascular experience with SK


1933: Tillett discovered SK
1941: Plasminogen isolated
1945: Plasmin isolated
1947: UK isolated
1957: Tissue plasminogen activator isolated
1987: Alteplase FDA approved
1996: Reteplase FDA approved
1999: UK removed from market
2000: Tenecteplase FDA approved
2002: UK reintroduced
1930
1940
1950
1960
1970
1980
1990
2000
1950: SK used to treat HTX
1955: SK first used in AMI
1973: UPET results on PE published
1986: GISSI results on AMI published
1994: Rochester/ STILE results on LE ischemia published
1995: NINDS results on AIS published

THROMBOLYTIC AGENTS

Thrombolytic agents can be classified into one of four groups:

- Plasminogen activators isolated from a biologic source {**Streptokinase, Urokinase** }
- Recombinant plasminogen activators and genetically modified variants to optimize thrombolysis {**Alteplase, Reteplase, Tenecteplase** }
- Novel plasminogen activators still under investigation {**Staphylokinase, Desmoteplase**}
- Direct-acting agents

First-Generation Thrombolytic Drugs

Not Fibrin Specific, *Streptokinase, Urokinase*

Second-Generation Thrombolytic Drugs

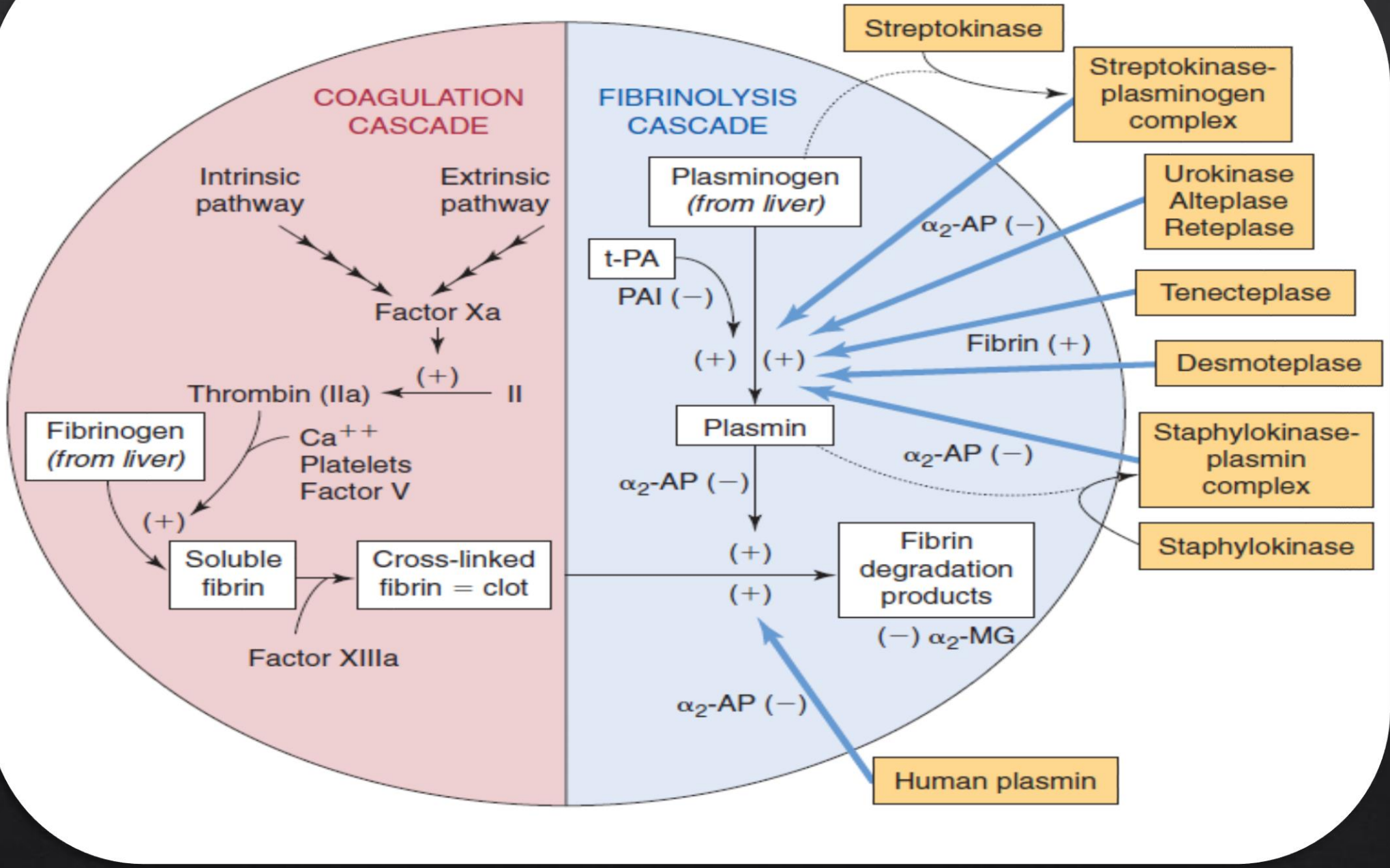
Fibrin Specific ,*Tissue Plasminogen Activator, Pro-urokinase*

Third-Generation Thrombolytic Drugs

Reteplase, Tenecteplase, Staphylokinase

The Ideal Thrombolytic Agent:

1. Fibrin specificity
2. Ease of administration
3. Rapid lysis time in a predictable dose-response pattern
4. Low cost
5. Monitoring with readily available laboratory tests(D-dimer, fibrinogen split products, fibrinogen, aPTT, PT, INR ⟹ indirectly assess the degree of thrombolysis and are unreliable indicators of thrombolytic effectiveness or predictors of hemorrhagic complications)


COAGULATION CASCADE
Intrinsic pathway
Extrinsic pathway
Factor Xa
(+)
Thrombin (IIa)
II
Fibrinogen (from liver)
Ca++
Platelets
Factor V
(+)
Soluble fibrin
Cross-linked fibrin = clot
Factor XIIIa
FIBRINOLYSIS CASCADE
Plasminogen (from liver)
t-PA
PAI (−)
(+)
(+)
Plasmin
α2-AP (−)
α2-AP (−)
(+)
(+)
Fibrin degradation products
(−) α2-MG
α2-AP (−)
Human plasmin
Streptokinase
Streptokinase-plasminogen complex
α2-AP (−)
Urokinase
Alteplase
Reteplase
Tenecteplase
Fibrin (+)
Desmoteplase
Staphylokinase-plasmin complex
Staphylokinase

Streptokinase

- Produced from Produced from β-hemolytic streptococci (the Lancefield group C *Streptococcus equisimilis)* ,Now recombinant technologies to produce SK via *Escherichia coli*.
- Complications , Bleedig in 15-20% of patients ,Fever ,Allergic Reactions and Tachyphylaxis.
- MOA Requires plasminogen as cofactor , Converts uncomplexed plasminogen to plasmin.
- Precise control of thrombolysis difficult ,Varied dose response per patient , separate half lifes(16 to 83 minutes)
- Despite its multiple FDA indications, it was rarely used in the United States because of its antigenicity and side effects.

The loading dose (units per milliliter x body weight in kilo- grams × blood volume (taken as 7 L). usually between 50,000 and 120,000 units

A maintenance dose was then given, starting at 1000 U/hr. This dose was increased or decreased depending on the results of coagulation studies 1000 to 8000

Urokinase

- Produced by renal tubular cells
- Direct,specific plasminogen activator ,Lack of circulating antibodies .
- Bleeding in 5-10% of patients
- Half life 14 minutes
- Significantly more expensive
- Approved for use in PE.
- Taken off market from 1999-2002 .

Recombinant Urokinase

- Saruplase and Nasaruplase.
- Most trials in acute MI and AIS.
- Higher incidence of intracranial hemorrhage .
- Prolonged half-life .

Initial dose: 4400 international units/kg IV at a rate of 90 mL/hr over 10 minutes

Maintenance dose: 4400 international units/kg/hr IV at a rate of 15 mL for 12 hours


TauroLock
Urokinase 25.000 IU
Catheter Lock Solu
TauroPharm GmbH, Ge
Store at 15
Cat./REF: TP-02
TauroLock™
10 mL Catheter Lock Solu
Store at 15–30°C
TauroPharm GmbH, Germ

Tissue Plasminogen Activator (t-PA)

- Originates from vascular endothelium .
- Sources { Recombinant DNA technology (rt-PA), melanoma cell line }
- The most commonly used thrombolytic agent in clinical practice.
- MOA Direct plasminogen activator ,High affinity for thrombus-bound fibrin ,Inhibits platelet aggregation.
- Half life 4-7 minutes.
- Recommended dosage 0.05 mg/kg/hr .
- **Alteplase,** Activase, Actilyse, Cathflo.


Actilyse®
Alteplase
50 mg
For fibrinolytic therapy
For i.v. infusion
Only on doctor's prescription
Harus dengan resep dokter
Reg. No. DKI9052500344A1
Boehringer
Ingelheim


Actilyse® 50 mg
For fibrinolytic therapy
For i.v. infusion
1 injection vial and 1 vial of solvent
Boehringer
Ingelheim
Actilyse® 50 mg
For fibrinolytic therapy
For i.v. infusion
Boehringer
Ingelheim
Sterile Water
Injection
50 ml to be used
reconstitute
Actilyse®
50 mg
Boehringer
Ingelheim

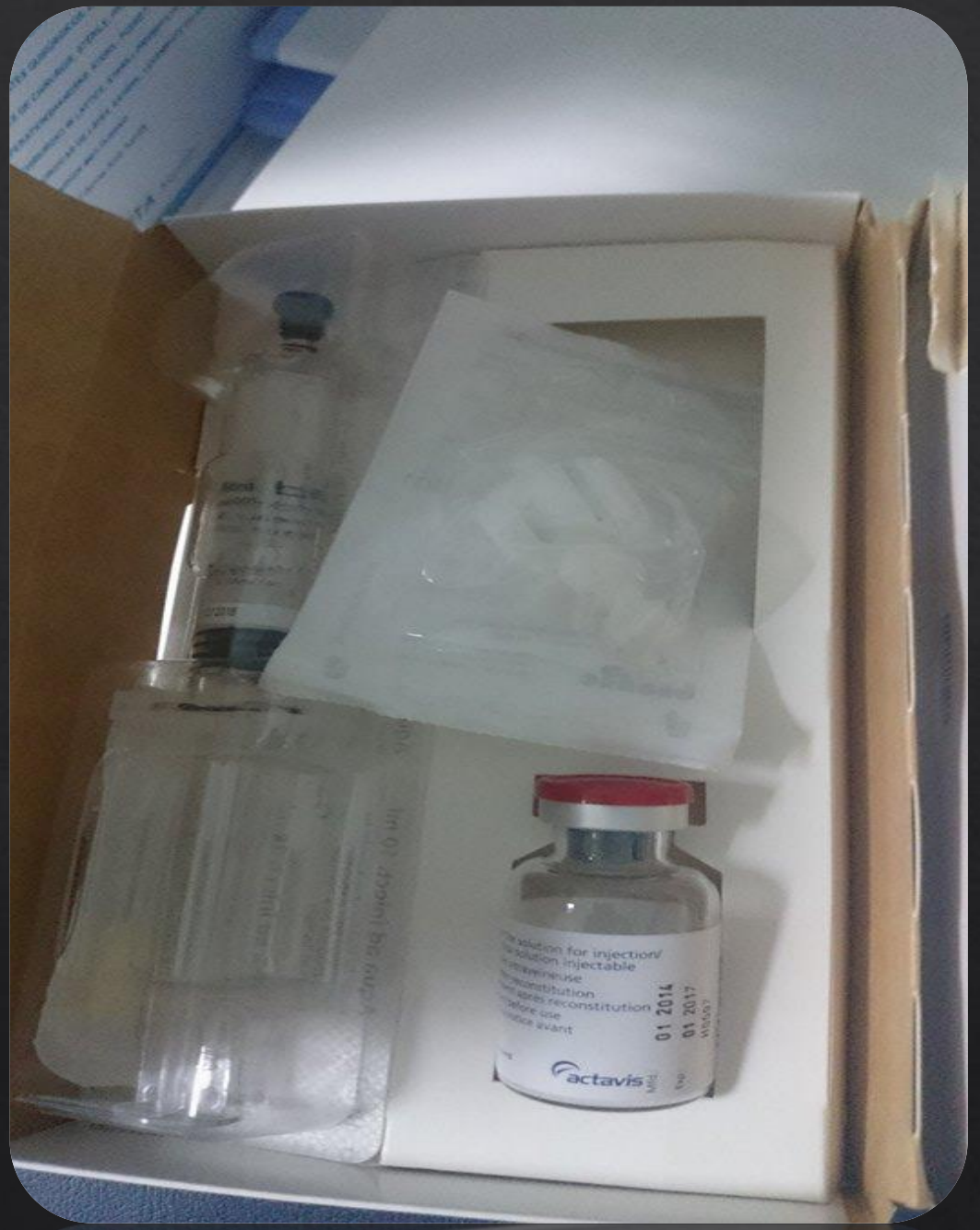

cathflo® activase®
(ALTEPLASE) 2 mg
For Use in Central Venous Access Devices
KEEP REFRIGERATED
Genentech
List No.: 13057
US License No.: 1048
NDC 50242-041-63
Cathflo® Activase®
(Alteplase)
NDC 50242-085-27
ALTEPLASE
ACTIVASE®
for intravenous use
100 mg (58 million IU)
a tissue plasminogen activator
US License No.: 1048
Genentech, Inc.
List No.: 8527
NDC 50242-044-13
ALTEPLASE
ACTIVASE®
for intravenous use
50 mg (29 million IU)
a tissue plasminogen activator
US License No.: 1048
Genentech, Inc.
List No.: 4413

Reteplase

- Decreased endothelial binding , Increased circulating levels.
- Decreased fibrin binding , Penetrates clot better with faster lysis
- Half life of 14-18 minutes .
- INJECT and GUSTO III Trials Compared reteplase to alteplase for MI { Reteplase showed increased flow rates (thrombolysis), No difference in mortality }
- Rapilysin, Retavase


Retavase®
Reteplase recombinant
Rx only
Centocor


actavis
Rapilysin®
Reteplasum
10 U
2 Injektionsflaschen mit Trockensubstanz
2 Spritzen mit Lösungsmittel
2 Rekonstitutionshilfen


actavis
01 2014
01 2017

Tenecteplase

- TPA mutant.
- High fibrin selectivity.
- Resistant to plasminogen activator inhibitors .
- Very effective in arterial thrombosis .
- Half life of 20-24 minutes .
- TNKase, Metalyse

SINGLE-BOLUS

TNKase®

Tenecteplase

For Fast Lytic Delivery in AMI


Metalyse® 10.000 U
Tenecteplase
Pulver und Lösungsmittel zur Herstellung einer Injektionslösung
Boehringer Ingelheim
1 Durchstechflasche mit Pulver zur Herstellung einer Injektionslösung
1 Fertigspritze mit Lösungsmittel zur Herstellung von Parenteralia
Bitte Anwendungshinweise sorgfältig beachten.
Nichtbeachtung kann dazu führen, dass eine höhere Dosis Metalyse
Metalyse® 10.000 U
Boehringer Ingelheim

Staphylokinase

- Plasminogen activator from S. aureus
- Does not cause systemic fibrinolysis.
- Half-life of staphylokinase is 7 minutes.
- High antigenicity.
- Not commercially available yet .

Desmoteplase

Direct-Acting Thrombolytic Agents

- The only direct-acting thrombolytic currently under investigation is human plasmin.
- Inhibited by circulating inactivators and therefore cannot be delivered systemically.
- Catheter-directed administration of these agents to the offending thrombus is required for therapeutic effect.

- Two forms of plasmin:

  γ-Plasmin (TAL-6003), a recombinant plasmin

  Human plasmin, It is obtained from donors

Application of Thrombolytics

- **Systemic/Intravenous Thrombolysis**
- **Catheter-Directed Thrombolysis**
- **CDT with Mechanical Thrombectomy**

Systemic/Intravenous Thrombolysis

- large doses of thrombolytic agent .
- An increased risk of hemorrhagic complications.
- Preservation of end organ function requires rapid delivery (AMI, AIS).

Catheter-Directed Thrombolysis

- the preferred method of delivery for ALI , DVT and AVG occlusion.
- CDT is the only delivery method that can be used with new thrombolytic agents (inactivated when systemically infused).
- An initial bolus is delivered via pulse spray technique followed by a continuous infusion for a specified period of time.

- The guide wire must traverse the occluded arterial or venous thrombosis, followed by placement of a multiple side-hole infusion catheter.
- Infusion catheter tip should not be placed past the thrombus.
- Administration of heparin to prevent propagation of thrombus around the indwelling catheter.
- APTT of 60 to 80 seconds should be achieved before thrombolysis.
- Once thrombolytic infusion has begun, the heparin dose should be decreased.(500 to 1000 U/hr via the delivery sheath).
- APTT should be monitored and heparin drip adjusted to maintain an aPTT 1.5 times control

Monitoring

- Pulse or the Doppler signal or improved symptoms.
- No existing laboratory test can directly monitor the degree and effectiveness of thrombolysis.
- D-dimer and fibrin degradation products are elevated when thrombolysis is ongoing.
- If fibrinogen levels drop below 100 mg/dL or the aPTT increases above 100 seconds, excessive consumption of coagulation factors is present and an increased risk of hemorrhagic complications exists, it is prudent to reduce or temporarily stop the lytic infusion until fibrinogen increases or the aPTT decreases, or both.

- Hemoglobin and plateletes monitors the possibility of clinically occult bleeding in the retroperitoneum or gastrointestinal tract.
- An increase in creatinine of 0.2 mg/dL is a sign of hypovolemia.
- Should be monitored in the intensive care unit, where samples for laboratory tests can be drawn at 4- to 6-hour intervals and patients assessed on an hourly basis.
- With CDT, serial angiography is performed through the indwelling catheter to access vessel patency at 6- to 12-hour intervals over a 24- to 48-hour period.

Complications

- **Hemorrhagic**
- **Antigenicity Related**
- **Catheter Related** (Dissection, Pseudoaneurysm, Emboli)
- **Embolic** (PE if DVT OR AVG , Distal in ALI)

ALI

Initial clinical improvement, with restoration of a pedal pulse or Doppler signal followed by sudden clinical deterioration ???

Contraindications

Absolute

(1) **Active internal bleeding**

(2) **Recent (within 2 months) cerebrovascular accident trauma, or intracranial or intraspinal surgery**

(3) **Known intracranial neoplasm**

(4) **Severe uncontrollable hypertension**

(5) **Uncontrollable clotting disorders**

(6) **Previous severe allergic reactions to the thrombolytic agent.**

Relative

(1)Recent (within 10 days) operative or obstetric procedures, biopsy or procedure in a location that is not compressible, gastrointestinal bleeding,or trauma, including cardiopulmonary resuscitation;
(2) left heart thrombus
(3) subacute bacterial endocarditis
(4) severe liver or kidney disease
(5) diabetic hemorrhagic Retinopathy
(6) acute pancreatitis
(7) pregnancy
(8) any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Intra-arterial Application

- Thrombosis after PTA
- Native Vessel Occlusion
- Acute Graft Occlusion
- Lower Extremity Ischemia
- Hemodialysis Access
- Acute Strok

Application of Venous

Table 36-7 Dosing of Currently Available Thrombolytic Agents for Venous Thrombosis

Agent	Dose
Alteplase†	Catheter directed: 0.25-2 mg/hr
Reteplase*†	Catheter directed: 0.75 U/hr
Tenecteplase*†	Catheter directed: 0.25-0.5 mg/hr

Dosages are for adult use (≈70 kg).

*These dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses.

†Infusions are stopped once no improvement is seen on serial venograms performed every 8 to 12 hours.

Deep Venous Thrombosis

- No Contraindications
- First Incidence
- Treatment Initiated < 5 Days of Symptoms
- Phlegmasia Cerulea Dolens

Axillary Vein Thrombosis

- Effort Thrombosis
- Younger Patients
- Poor Resolution with Anticoagulation
- Thrombolysis Indicated for Short Symptom
- Systemic and Local Infusion Equally Effective
- Post-Treatment Evaluation for TOS

Superior Vena Cava Thrombosis

- **Mediastinal Etiologies** Poor Response Cancer Trauma Infection
- **Catheter-Induced Thrombosis** Response Dependent on Duration of Symptoms
- **Idiopathic SVC Thrombosis (4%)** Good Respons

Patient Selection of Intra-arterial Patient Selection of Intra-arterial Thrombolytics

- Low doses of thrombolytic administered close to thrombus (Minimizes systemic effects, Dissolution of thrombus requires 12-72 hrs of therapy)
- Ensure viability of ischemic tissue (Shouldn't do in patients with neurologic affected
- Indications High surgical risk of morbidity/mortality Poor surgical outcome Multiple previous surgeries Adjunct to surgery

Table 36-6 Dosing of Currently Available Thrombolytic Agents for Acute Limb Ischemia

Agent	Dose
Alteplase	Catheter directed: Low-dose (extended infusions >12 hr): 0.5-2.5 mg/hr High-dose: 0.05 mg/kg/hr up to 12 hr (or until maximum of 100 mg administered)
Reteplase*	Catheter directed: 2-U bolus, then infuse 0.5–1 U/hr (should not exceed a total administered dose of 20 U)
Tenecteplase*	Catheter directed: 0.25-0.5 mg/hr; infusion stopped if no improvements on serial arteriograms

Dosages are for adult use (≈70 kg).

*These dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses.

Popliteal Artery Occlusion with Distal Clot

- Poor surgical result
- Amputation risk – 40%
- Moderate Ischemia : Trial of Lytic Therapy
- Severe Ischemia Severe Ischemia : Surgical Exploration with Intraoperative Intra-arterial Lysis

Acute Graft Occlusion

Table 36-8	Dosing of Currently Available Thrombolytic Agents for Arteriovenous Graft Occlusion
Agent	**Dose**
Alteplase*†	Catheter directed: 2 mg
Reteplase*†	Catheter directed: 1 U
Tenecteplase*†	Catheter directed: 1 mg

Dosages are for adult use (≈70 kg).

*These dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses.

†The listed dosages are administered under fluoroscopic guidance. Dosing can be repeated if arteriovenous graft patency is not restored.

Indications for Intraoperative Thrombolytics

- 30% of embolectomies are incomplete :
  - Residual intravascular defects seen on completion angiography
  - Further mechanical manipulation increases thrombogenicity
- Bulk of thrombus removed , less lysis needed

Table 36-9	Dosing of Currently Available Thrombolytic Agents for Catheter Occlusion
Agent	**Dose**
Alteplase[†]	≥30 kg: 2 mg in 2 mL; may repeat after 120 min if catheter still occluded <30 kg: 110% of the internal lumen volume (not to exceed 2 mg in 2 mL); may repeat above after 120 min if catheter still occluded
Reteplase[*†]	0.4 U in 2 mL; may repeat after 30-60 min if catheter still occluded

Dosages are for adult use (≈70 kg).

*These dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses.

[†]The volume instilled is not to exceed the internal lumen volume. Clamp the catheter and try to aspirate its contents in 30 minutes. If no result, a second dose can be attempted (see individual agents for timing).


Take Home Message

- Alteplase commonly used.
- Begin TPA at 0.5-1 mg/hour .
- Optimally used in occlusions of <7 days duration
- Obtain baseline fibrinogen, PTT and Repeat in 12 hours then daily.
- Expect fibrinogen to drop and PTT prolonged in 50% (suggests lytic state) .
- No specific parameters correlate with bleeding.
- If no progress made and no evidence of bleeding, can increase dosage to 1+ mg/hour
- Heparin administration
    - Recommended to prevent peri-catheter thrombosis
    - Aim for PTT 1.5-2x normal
    - Attempt to run through sheath in affected
    - Usually run at 500-1000 unit/hour
    - PTT should not exceed 60 sec
- Surgery required, give FFP to normalize fibrinogen level fibrinogen level.

Thank you for listening!