Thrombolytic drugs

by

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**Antithrombotics**

- **Anticoagulant** (for Venous & arterial thrombosis)
  - UFH
  - ATIII
  - LMWH
- **Antiplatlets** (for arterial and intracardiac thrombosis)
  - X:
  - DTIs

**Fibrinolytics** (for arterial & venous thrombosis)
- Non-fibrin-specific: 
  - SK + Plasminogen
  - APSAC
  - Plasminogen-SK activator complex
- Fibrin-specific: 
  - t-PA
  - e-PA
  - Bat-PA
  - scu-PA

**Antithrombotics**

- **Antithrombosis**
  - Heparin (Xa and IIa)
  - Enoxaparin (Xa > IIa, 3:1)
  - Fondaparinux (Xa only)

**Antiplatlets** (for arterial and intracardiac thrombosis)

- Thrombin also mediates platelet activation via the PAR 1 receptor.
- Fibrinogen mediates platelet-to-platelet cross-linkage via activated GP IIb/IIIa receptors.
Anticoagulant action of HEPARIN

UFH

Unfractionated heparin

Antithrombin

Factor Xa

Thrombin

LMWH

Low-molecular-weight heparin

Antithrombin

Factor Xa
Rationale for Antithrombotic Therapy

**Thrombogenesis**
- Vascular injury
  - Platelet adherence and activation
    - Thrombin generation and fibrin formation
      - Plasmin generation and fibrinolysis

**Therapy**
- Reduce risk factors
- Platelet inhibitors
- Anticoagulants
- Fibrinolytics
THROMBOLYTIC DRUGS

Pathophysiologic Rationale

- Re-establishing coronary flow during a period of occlusion will limit myocardial infarct (MI) size was first demonstrated in a dog model of MI by Reimer et al. in 1977.
- These experiments demonstrated that after coronary occlusion there was a wavefront of ischemic cell death, which progressed over time from the subendocardium toward the epicardium.
- The time frame for this process was quite short, in the range of 3 to 4 hours.
- Thus these studies provided the basis for the rationale that re-canalization and reperfusion early in the course of MI would limit myocardial necrosis, improve left ventricular function, & improve patient outcome.
Wave-front Phenomenon of Ischemic Cell Death
THROMBOLYTIC DRUGS

Pathophysiologic Rationale

• Angiographic studies in the early 1980s showed that early in the course of MI with ST-segment elevation, most patients had complete coronary occlusion.

• Pathologic studies established the importance of plaque rupture in the pathogenesis of acute coronary syndromes.
Acute coronary syndromes varies with the degree of thrombus-induced obstruction, ranging from a persistent complete occlusion corresponding to ST-segment elevation MI to a subocclusive thrombus corresponding to unstable angina.
Thrombolytic Therapy Benefit

• The ability of streptokinase to lyse clots was first recognized in the 1930s.
• Thrombolytic therapy was not applied to acute MI until the early 1980s after the establishment of the central role of acute thrombotic coronary occlusion in the pathogenesis of acute MI.
• Clinical trials have firmly established the benefit of thrombolytic therapy for patients with acute MI with ST-segment elevation within 12 hours of symptom onset.
• Patients with unstable angina or MI without ST elevation do not benefit from thrombolytic therapy.
• Rapid initiation of thrombolytic therapy is essential to optimize patient outcome because each additional hour of delay from symptom onset to treatment corresponds to a 0.5% to 1% increase in mortality.
Characteristics of the Ideal Fibrinolytic Agent

- Longer half-life/single-bolus administration
- Increased fibrin specificity/decreased bleeding and ICH
- More rapid and consistent achievement of TIMI grade 3 flow
- No effect on blood pressure
- No antigenicity
- Lower re-occlusion rates
- Greater resistance to PAI-1
- Compatible with other intravenous agents
- Low cost

Fibrinolysis

**Plasminogen As**

- **Secretion:** Urine (UK, u-PA), Bile, bilokinase, Latex, saliva, tear
- **Vascular endothelium:** t-PA, u-PA
- **Tissue:** lung, prostate, uterus, RBC, Platelet
- **Exogenous pathway:** IIa, XIIa, Ixa, KK

**Exogenous (thrombolytic):** Streptokinase (SK), Urokinase (UK), rt-PA include alteplase, reteplase & tenecteplase (TNKase)

**Plasminogena Is**

- PAI-3
- PAI-1
- PAI-2

**Plasmin Is**

- $\alpha_2$-plasmin inhibitor ($\alpha_2$-PI)
- $\alpha_2$-macroglobulin ($\alpha_2$-MG)

**Fibrinolysis**
Coagulation and Fibrinolysis

Fibrinolysis
- Injured endothelial cells
- Plasminogen activators
- Plasmin cleaved from plasminogen
- Fibrin degrades
Fibrinolytic agents

First-generation
Streptokinase Streptase, Kabinase, Urokinase Abbokinas

Second-generation
Alteplase (tissue plasminogen activator, t-PA) Activase
Anistreplase (APSAC) Eminase
Prourokinase (scu-PA)*

Third-generation
Reteplase (r-PA) Retavase
Tenecteplase (TNK-t-PA) TNKase
Lanoteplase* (n-PA)
Staphylokinase* (SAK 42D)
Antibody-targeted PAs*
Vampire bat-PA*
Alfimeprase*
*Not approved for clinical use
Mechanism of Thrombolytic Drugs

- The plasmin(ogen) molecule has lysine binding sites, which bind to and degrade fibrin.
- Fibrin-specific agents are much more active upon binding to fibrin, thereby increasing the affinity for plasminogen at the clot surface.
MECHANISMS OF ACTION OF AVAILABLE AGENTS

CIRCULATION
- Circulating plasminogen
  - STREPTOKINASE (SK)
    - SK-Plasminogen complex
    - UROKINASE
    - ACTIVASE® (Alteplase)
    - Circulating plasmin
      - Fibrinogen degradation
        - Production of FDPs

CLOT
- Fibrin-bound plasminogen
  - Thrombolysis

Moderate activity
Minimal activity
Substantial activity
Mechanism of Thrombolytic Drugs

Fibrin Specificity

$t$-PA\textsubscript{(alteplase)}

$\rightarrow$

$n$-PA\textsubscript{(lanoteplase)}

<table>
<thead>
<tr>
<th>SK</th>
<th>r-PA/n-PA</th>
<th>t-PA</th>
<th>TNK-tPA</th>
</tr>
</thead>
</table>
### Thrombolytic Agents: Current Status

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Streptokinase (SK)</strong></td>
<td><strong>Antigenic</strong></td>
</tr>
<tr>
<td>1.5M units up to 1 hour</td>
<td><strong>Allergic reactions</strong></td>
</tr>
<tr>
<td>Proven mortality reduction and myocardial salvage</td>
<td><strong>Hypotension</strong></td>
</tr>
<tr>
<td>Aspirin enhances benefit</td>
<td><strong>APSAC</strong></td>
</tr>
<tr>
<td>Serious bleeds infrequent</td>
<td><strong>30 units over 2-5 min</strong></td>
</tr>
<tr>
<td>Inexpensive</td>
<td>Proven mortality reduction</td>
</tr>
<tr>
<td></td>
<td>Brief injection</td>
</tr>
<tr>
<td></td>
<td>Better fibrin binding than SK and longer action in vivo</td>
</tr>
<tr>
<td></td>
<td>Serious bleeds infrequent</td>
</tr>
<tr>
<td></td>
<td>Rethrombosis rate low</td>
</tr>
</tbody>
</table>

Sol Sherry, M.D./1988
### Thrombolytic Agents: Current Status

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urokinase (UK)</strong></td>
<td>Non-antigenic</td>
<td>Very expensive</td>
</tr>
<tr>
<td></td>
<td>Low rethrombosis rate</td>
<td>Benefit data needed</td>
</tr>
<tr>
<td></td>
<td>Serious bleeds infrequent</td>
<td></td>
</tr>
<tr>
<td><strong>Prourokinase</strong></td>
<td>Non-antigenic</td>
<td>Very expensive</td>
</tr>
<tr>
<td>(scu-PA)</td>
<td></td>
<td>Delayed action</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insufficient data to evaluate</td>
</tr>
<tr>
<td><strong>rt-PA</strong></td>
<td>Non-antigenic</td>
<td>Very expensive</td>
</tr>
<tr>
<td>100 mg over 3 hours</td>
<td>Proven mortality reduction and myocardial salvage</td>
<td>Long infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cerebral bleeds a problem</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frequent rethrombosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Early angioplasty required</td>
</tr>
</tbody>
</table>
## Summary of Selective Thrombolytic Agents

<table>
<thead>
<tr>
<th></th>
<th>Alteplase</th>
<th>Tenecteplase</th>
<th>Reteplase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>100 mg IV infusion over 2 hours</td>
<td>Weight-adjusted IV bolus over 5-10 sec <em>(APPENDIX C)</em></td>
<td>10 units IV bolus x 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial: 20-24 mins</td>
<td>30 mins apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Terminal: 90-130 mins</td>
<td></td>
</tr>
<tr>
<td><strong>T ½</strong></td>
<td>&lt;5 mins</td>
<td>13-16 mins</td>
<td></td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic and renal</td>
</tr>
<tr>
<td><strong>Fibrin specificity</strong></td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>FDA approved for MPE?</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td>Bleeding complications biggest limitation to therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intracranial hemorrhage most devastating</td>
<td></td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td></td>
<td><em>(APPENDIX D)</em></td>
<td></td>
</tr>
</tbody>
</table>

*FDA = Food and Drug Administration; IV = intravenous; mins = minutes; sec = seconds*
### Characteristics of alteplase compared with the third-generation fibrinolytic drugs

<table>
<thead>
<tr>
<th></th>
<th>Alteplase</th>
<th>Tenecteplase</th>
<th>Retepase</th>
<th>Staphylokinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight (kD)</td>
<td>70</td>
<td>70</td>
<td>39</td>
<td>16.5</td>
</tr>
<tr>
<td>Half-life (min)</td>
<td>4–8</td>
<td>20–24</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Fibrin specificity</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Weight-adjusted</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Pending</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 67 kg</td>
<td>1.25 mg/kg*</td>
<td>&lt; 60 kg: 30 mg</td>
<td>10 million units x 2, 14–45 mg</td>
<td></td>
</tr>
<tr>
<td>&gt; 67 kg</td>
<td>100 mg†</td>
<td>60–69.9 kg: 35 mg</td>
<td>30 minutes apart</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>70–79.9 kg: 40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>80–89.9 kg: 45 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 90 kg: 50 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TIMI grade 3 flow rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 90 minutes (%)</td>
<td>50–60</td>
<td>50–64</td>
<td>50–60</td>
<td>60–65</td>
</tr>
<tr>
<td><strong>Intracranial hemorrhage (%)</strong></td>
<td>0.62–0.94</td>
<td>0.93</td>
<td>0.77–1.2</td>
<td>Not well studied</td>
</tr>
</tbody>
</table>

*15 mg bolus over 1–2 minutes, then 0.75-mg/kg infusion (50-mg maximum) over 30 minutes, followed by 0.5-mg/kg infusion (35-mg maximum) over 60 minutes
†15 mg over 1–2 minutes, then 50 mg over 30 minutes and 35 mg over 60 minutes
# Fibrinolytics in Development: Comparative Overview

<table>
<thead>
<tr>
<th></th>
<th>Tenecteplase (TNK-tPA)</th>
<th>Lanoteplase (n-PA)</th>
<th>Staphylokinase</th>
<th>Saruplase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Half-life (minutes)</strong></td>
<td>20</td>
<td>37</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Single bolus</td>
<td>Single bolus</td>
<td>2 boluses</td>
<td>Bolus + 60-min infusion</td>
</tr>
<tr>
<td><strong>Provides patient-specific weight-based dosing</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td><strong>Fibrin specificity</strong></td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>PAI-1 resistance</strong></td>
<td>Increased</td>
<td>??</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td><strong>Antigenic</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Plasminogen activation</strong></td>
<td>Direct</td>
<td>Direct</td>
<td>Indirect</td>
<td>Direct</td>
</tr>
</tbody>
</table>
Thrombolytic drugs – major drawbacks

- Treatment is limited to acute in-hospital treatment. There is a high risk of bleeding inherent in this treatment.
- Patients using anticoagulants are contraindicated for treatment with thrombolytics.
Risks

Plasmin breaks down fibrin = fibrin degradation products (FDPs).

FDPs compete with thrombin = slow down the conversion of fibrinogen to fibrin (and thus slows down clot formation).

Secondary impact tPA – binds circulating plasminogen

Lysis of normal haemostatic plugs - bleeding

Intracranial haemorrhage, absolute risk is increased 6% in patients of first 10 days, maximal during the first 36 hours after treatment. (c.f. 3 month overall risk reduction of 11% )

Potential interactions with anticoagulants, ACE inhibitors, platelet function altering drugs etc.

Cholesterol embolisms

Immune problems – plasmin also cleaves C3 component of complement system
Uses of Thrombolytics:

1) Coronary Thrombolytics
2) Pulmonary embolism
3) DVT
4) Arterial occlusion e.g. Popliteal artery
5) Ischaemic stroke
6) Occluded AV shunts
7) Blocked central vacuum catheters
Contraindications to Thrombolytic Therapy

- **Absolute contraindications include:**
  - Recent head trauma (3 months) or cranial tumor
  - Previous hemorrhagic shock
  - Stroke or cerebro-vascular events, Intracranial hemorrhage 1 year old
  - Major surgery within two weeks
  - Ischemic Stroke within 3 months
  - Known structural cerebrovascular lesion (AVMs, aneurysms, tumor)
  - Aortic dissection
  - Severe uncontrolled hypertension SBP > 180 DBP > 110
  - Active bleeding or bleeding diathesis
  - Acute pericarditis

- **Relative contraindications include:**
  - Active peptic ulcer, diabetic retinopathy, pregnancy, uncontrolled HTN
Haemostatic agents

1) E – aminocaproic acid, Tranexamic acid – Urinary tract bleeding, prostatic surgery tonsillectomy, Clinical menorrhagia, vWD, hemophilia patients with tooth extraction
2) Aprotinin – Cardiac surgery

Topical absorbable haemostatic

1) Thrombin
2) Microfibrillar collagen hemostat
3) Absorbable gelatin–Sponge film and powder, oral–G.I, bleeding
4) Oxidized cellulose -physical effect - requires phagocytosis
Contraindications to Antithrombotic Therapy

• Specific to warfarin (ambulatory patients)
  - Early and late pregnancy
  - Poor patient cooperation, understanding, reliability
  - Unsatisfactory laboratory or patient follow-up
  - Occupational risk to trauma
Contraindications to Antithrombotic Therapy

• Specific to thrombolytic agents
  - Recent thoracic, abdominal, or central nervous system surgery
  - Recent cerebrovascular accident, trauma, or neoplasm
  - Bleeding ulcer
  - Hypertension
  - Anticipated invasive procedures (arterial punctures, biopsies, central lines)
  - Concurrent hemostatic dysfunction
Fibrinolytic Inhibitors

- **Aminocaproic Acid & tranexamic cid**
  - They have lysine-like structure
  - They inhibit fibrinolysis by competitive inhibition of plasminogen activation
  - Adjuvant therapy in hemophilia, fibrinolytic therapy-induced bleeding & postsurgical bleeding

- **Aprotinin** is a serine protease inhibitor
  - It inhibits fibrinolysis by free plasmin
  - Used to stop bleeding in some surgical procedures