Stroke and the Use of tPA

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Objectives

Stroke
- What is Stroke?
- Risk Factors
- Two Types
Alteplase (recombinant tPA)
Alteplase for Stroke
- Ischemic Strokes
- Window of Time
- Precautions
Preparation of Alteplase
Unused Alteplase

Stroke - What is a Stroke?

- Stroke is the same as a Brain attack
- Stroke occurs when a portion of the brain is deprived of oxygen
Stroke - What is a Stroke?

In the United States: 1,2
– Stroke affects 795,000 yearly
– Of those, 137,000 die
  • 1 of every 18 deaths
  • #4 cause of death
  • 1 death every 4 min
– Gender incidence
  • 40% in males
  • 60% in females

For 2006, in the United States, stroke death rates per 100,000 people: 2
– White males: 41.7
– White females: 41.1
– Black males: 67.7
– Black females: 57.0

Stroke is the leading cause of disability 2
– In 2010: $73.7 B

“Patients see severe stroke disability as similar to or worse than death.” 4

Risk Factors

For 2006, in the United States, stroke death rates per 100,000 people: 2
– White males: 41.7
– White females: 41.1
– Black males: 67.7
– Black females: 57.0
### Nonmodifiable Risk Factors: 2
- **Age**
  - Each decade after age 55, risk doubles
- **Hereditary presence of stroke**
  - Specifically: parents, grandparents, and siblings
- **Race**
  - African-Americans have a much higher risk than Whites
- **Gender**
  - Women experience more strokes than men
  - Men are more likely than women to die from a stroke
- **Prior stroke, transient ischemic attack (TIA), and heart attack**

### Modifiable or Treatable Risk Factors: 2
- **High blood pressure**
- **Cigarette smoking**
- **Diabetes**
  - Diabetics often have high blood pressure, high cholesterol, and are overweight, which are all risk factors
- **Carotid and other artery disease**
- **Peripheral artery disease**
- **Atrial fibrillation**
- **Other heart disease**
  - Including: heart failure, dilated cardiomyopathy, and congenital heart defects

### Other Interesting Risk Factors: 2
- **Southeast United States**
  - Considered the "stroke belt"
- **Sickle cell disease**
- **High cholesterol**
- **Poor diet**
  - Diets high in saturated and trans fats
  - Diets high in cholesterol
  - Diets high in Na, which can elevate blood pressure
  - Diets with excess calories can lead to obesity
- **Physical inactivity and obesity**
- **Drug abuse**
  - Most commonly associated: cocaine, amphetamines, and heroin
  - Strokes in this group are often seen in a younger population
When medical first responders believe a patient may have had a stroke, they will:

1) Conduct the Cincinnati Stroke evaluation
2) Ask those who are with the patient when their “last known normal” was

• Cincinnati Prehospital Stroke Scale (CPSS) 5
  – A tool for first medical responders to evaluate if a patient has had a stroke
  – Consists of 3 parts:
    1) Facial Droop
    2) Arm Drift
    3) Speech
  – Of all stroke patients, 66% have at least 1 of the 3 deficits

• American Stroke Association 2

Two Types
First, a couple of definitions:

- **Infarct**: Area of necrosis resulting from a sudden insufficiency of blood supply.
- **Ischemia**: Mechanical obstruction of blood supply resulting in organ dysfunction.

**1) Ischemic Stroke**
- A clot obstructs the flow of blood to the brain.
- Accounts for 87% of all strokes.

**Stroke - TWO TYPES**

Image from Activase.com (3/14/2013)

**Stroke - TWO TYPES**

First, a couple of definitions:

- **Infarct ~ Dead**
- **Ischemia ~ Dying**

Image from Activase.com (3/14/2013)

**1) Ischemic Stroke**
- If the blood flow doesn’t resume within 3 hours, a stroke in the bloodstream to the brain.
### Stroke - TWO TYPES

#### 1) Ischemic Stroke

![Image from StrokeAssociation.org (3/13/2013)](https://example.com/ischemic-stroke-image)

- A weakened blood vessel ruptures, which prevents blood flow to the brain
  
  1) Intracerebral Hemorrhage (ICH): The ruptured vessel bleeds into the tissue deep within the brain
  - Accounts for 10% of all strokes
  
  2) Subarachnoid Hemorrhage (SAH): The ruptured vessel is on the surface of the brain, spilling blood between the brain and the skull
  - Accounts for 3% of all strokes

#### Transient Ischemic Attack (TIA)

- Also known as a “mini stroke” or “warning stroke”
- Only difference between an ischemic stroke and a TIA is that a TIA is temporary
- The onset of symptoms in TIA is rapid and the same as an ischemic stroke
- Resolution of symptoms signifies elimination of the immediate blockage

#### 2) Hemorrhagic Stroke

- A weakened blood vessel ruptures, which prevents blood flow to the brain
  
  1) Intracerebral Hemorrhage (ICH): The ruptured vessel bleeds into the tissue deep within the brain
  - Accounts for 10% of all strokes
  
  2) Subarachnoid Hemorrhage (SAH): The ruptured vessel is on the surface of the brain, spilling blood between the brain and the skull
  - Accounts for 3% of all strokes

![Image from StrokeAssociation.org (3/13/2013)](https://example.com/hemorrhagic-stroke-image)
Stroke - TWO TYPES

2) Hemorrhagic Stroke – ICH

Other ailments that may appear stroke-like include:
1) Seizure
2) Migraine with an aura
3) Syncope
4) Less common causes include:
   • Total global amnesia; Metabolic disturbances (e.g. hypoglycemia); multiple sclerosis; brain tumors; hepatic, renal, and pulmonary encephalopathies; psychiatric disturbances; and many more

2) Hemorrhagic Stroke – SAH

Why is the cause of the stroke symptoms important?

Treatment depends on what caused the stroke
Alteplase (recombinant tPA)

**Pharmacologic class:** Thrombolytic agent

**Mechanism of action:**

- Initiates local fibrinolysis by binding to fibrin in a thrombus (clot) and converts entrapped plasminogen to plasmin

**Brand Names**

- Activase®
- Cathfio® Activase®

**Name confusion**

- Alteplase is NOT Altace®
- tPA / Alteplase / Activase® is NOT Tenecteplase / TNKase®

**Pharmacodynamics / Pharmacokinetics**

- **Duration:**
  - At 5 minutes after infusion termination, more than 50% has been cleared from the plasma
  - At 10 minutes, about 80% has been cleared

- **Excretion:**
  - Rapidly cleared by the liver

**Dose adjustments for kidney or liver impairment:** None

No generic alternatives available
Alteplase (recombinant tPA)

In the body:
1) Plasminogen is converted to plasmin by tPA
2) Plasmin breaks down fibrin connections
3) Disintegration of fibrin breaks down a clot

Alteplase (Activase®) is the synthetic form of tPA

Alteplase for Stroke - ISCHEMIC STROKES

- When alteplase was given within 3 hours of last known normal: 8
  - At 3 months, there was complete or near complete recovery:
    - For placebo, in 21% of patients
    - For alteplase, in 38% of patients
Alteplase for Stroke - ISCHEMIC STROKES

• When alteplase was given within 3 hours of last known normal: 8,9

![Graph showing mortality rates with and without alteplase treatment.](image)

Alteplase for Stroke - WINDOW OF TIME

### Alteplase for Stroke

Window of Time

| Estimated time of acute ischemic insufficiency in a typical large vessel occlusion ischemic stroke |
|-------------------------------|----------------|----------------|
| Neuronal | Accelerated aging |
| Every second | 24,000 | 6.7 hours |
| Every minute | 1 million | 11 weeks |
| Every hour | 100 million | 3.5 years |
| 15 hours | 1.9 million | 36 years |
Many alteplase studies focused on a 3 hour window
- Further analyses demonstrated that administration at 90 minutes resulted in better outcomes than when administered at 180 minutes. 11
- Another study found that administration at 3 hours was better than at 4.5 hours. 12
- If you wait until 6 hours: 13,14
  - No better outcomes than placebo
  - More intracranial hemorrhage

The number of patients with ischemic stroke that must be treated with alteplase to achieve one favorable outcome is: 15
- If administered between 0 and 1.5 hours: 5
- If administered between 1.5 and 3 hours: 9
- If administered between 3 and 4.5 hours: 15

Key point:
Administer as soon as possible

In addition, it is not currently recommended to administer beyond 4.5 hours of last known normal
Alteplase for Stroke - WINDOW OF TIME

Meeting the time requirement can be a challenge:
1) Recognize the symptoms of a stroke
   • Someone must be with the patient
   • Many stroke victims are identified after they lay down for a rest
2) Contact emergency services
3) Evaluate the patient
4) Transport the patient

Meeting the time requirement can be a challenge:
– Once at the hospital:

   Image from Activase.com (3/14/2013)

Alteplase for Stroke - PRECAUTIONS

Must consider:
1) What are the risks to thrombolytic treatment?
2) What are the benefits to thrombolytic treatment?
3) When is treatment too late to save the affected brain tissue?
4) When do the risks outweigh the benefit?
Alteplase for Stroke - PRECAUTIONS

In the United States: 16

- Of all ischemic strokes, 22% present to an emergency department within 3 hours
- Of all ischemic strokes, only about 8% meet eligibility criteria for alteplase

Alteplase for Stroke - PRECAUTIONS

Contraindications for use in ischemic stroke:

In summary, anything that increases the risk of a major bleed

- Evidence of ICH or suspicion of SAH on pretreatment evaluation
- Intracranial or intraspinal surgery within past 3 months
- Stroke or serious head injury within past 3 months
- History of intracranial hemorrhage
- Uncontrolled hypertension
  - Systolic > 185 mm Hg
  - Diastolic > 110 mm Hg
- Seizure at the onset of stroke
- Active internal bleeding
- Intracranial neoplasm
- Arteriovenous malformation or aneurysm
- Multilobar cerebral infarction
- Known bleeding issues, including:
  - Use of oral anticoagulants (Unless INR ≤ 1.7)
  - INR > 1.7 (or PT > 15 seconds)
  - Administration of heparin in last 48 hours WITH elevated aPTT
  - Platelet count < 100,000/mm³

When administered, must monitor: 6

1) Neurologic exam
   - At baseline
   - Every 15 minutes during alteplase infusion
   - Every 30 minutes, for next 6 hours
   - Every 1 hour until 24 hours after administration

2) Blood pressure
   - At baseline
   - Every 15 minutes for first 2 hours
   - Every 30 minutes for next 6 hours
   - Every 1 hour until 24 hours after administration
   - If systolic > 180 mm Hg OR diastolic > 105 mm Hg, administer antihypertensives
### Alteplase for Stroke - PRECAUTIONS

**When administered, must monitor:**

3) Head CT scan
   - At baseline
   - At 24 hours, before starting anticoagulants
4) CBC at baseline
5) aPTT at baseline
6) PT/INR at baseline
7) Glucose at baseline

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### Alteplase for Stroke - PRECAUTIONS

**When administered, must monitor:**

- Stop the infusion and obtain an emergency CT scan if the patient experiences any of the following:
  - Severe headache
  - Nausea
  - Vomiting

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### Alteplase for Stroke - PRECAUTIONS

**Adverse reactions that occur 1 to 10% of the time:**

- Hypotension
- Fever
- Bruising
- GI hemorrhage
- Nausea, vomiting
- Genitourinary hemorrhage
- Bleeding in general (0.5% is major; 7% is minor)
- Bleeding at catheter puncture site (15%)

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### Alteplase for Stroke - PRECAUTIONS

**Other significant adverse reactions:**

- Cerebral edema
- Cerebral herniation
- Seizure
- New ischemic stroke
Preparation of Alteplase

Reconstitution: 6,9

- Mix by gently swirling or slow inversion — Avoid agitation
  - Not compatible with preservatives or D5W

- Solution should be:
  - Transparent
  - Clear or pale yellow

- Final concentration: 1 mg/mL

Reconstitution: 6,9

- 50 mg Vial
  - Vial is under vacuum
  - Use provided diluent (sterile water)

- 100 mg Vial
  - Vial is without vacuum
  - Use transfer set with provided diluent (sterile water)

Solution should be:
- Transparent
- Clear or pale yellow

Final concentration: 1 mg/mL

Use within 8 hours

Can freeze (−20°C) and store for up to 6 months

Do not shake or send through tube system
Preparation of Alteplase

Dose for acute ischemic stroke

- Recommended dose:
  - Total dose: 0.9 mg/kg (maximum of 90 mg)
  - Load 10% of total dose over first 1 minute
  - Administer remaining 90% of dose over next 60 minutes

- Example, patient is 110 kg:
  - Total dose is 90 mg
  - Load patient with 9 mg
  - Then administer 81 mg over next 60 minutes

Preparation of Alteplase

Be aware of what alteplase is being used to treat

There are other FDA-approved indications:

- ST-elevated myocardial infarction (STEMI)
  - Up to 100 mg over 1.5 hours

- Acute massive or submassive pulmonary embolism (PE)
  - 100 mg over 2 hours

- Central venous catheter clearance
  - 2 to 4 mg to clear a clogged catheter

Unused Alteplase

What if you prepare a dose for stroke reversal and it is not administered?

Unused alteplase can be returned to Genentech® for replacement

- Information at Activase.com can provide more information

- At Saint Alphonsus we contact our Activase® representative for returns
Unused Alteplase

Alteplase Reimbursement:

- Genentech requires the entire contents from the vial for reimbursement
- Genentech will replace what was not used, BUT it will take several weeks for the replacement to arrive

Summary

1) Alteplase can be administered in patients who have suffered an ischemic stroke within the previous 4.5 hours, and do not have a significant bleed risk

2) For stroke, alteplase is dosed at 0.9 mg/kg, with a maximum dose of 90 mg

3) To replace a prepared, unused dose of alteplase, save the entire amount of alteplase and contact your Activase® representative

References

References