

Stroke and the Use of tPA

ISHP Spring Conference
6 April 2013

Jeremy Crowfoot, PhD, PharmD
Pharmacist Resident
Saint Alphonsus Regional Medical Center, Boise, ID

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 - 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

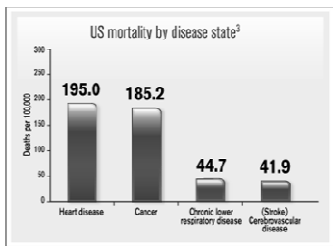


Image from Activase.com (3/14/2013)

Stroke - WHAT IS A STROKE?

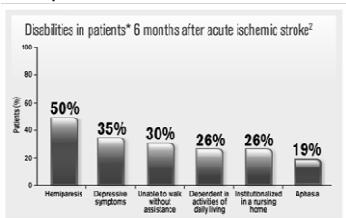
For 2006, in the United States, stroke death rates per 100,000 people: 2

- White males: 41.7
- White females: 41.1
- Black males: 67.7
- Black females: 57.0

Stroke - WHAT IS A STROKE?

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

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

Stroke

Risk Factors

Stroke - RISK FACTORS

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**

Stroke - RISK FACTORS

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

Stroke - RISK FACTORS

Modifiable or Treatable Risk Factors: ²

- **Sickle cell disease**
 - Causes red blood cells to be more sticky
- **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**

Stroke - RISK FACTORS

Other Interesting Risk Factors: ²

- **Southeast United States**
 - Considered the "stroke belt"
- **Socioeconomic factors**
 - Strokes are more common in low-income populations
- **Alcohol abuse**
 - Recommend men not exceed 2 drinks per day
 - Recommend nonpregnant women not exceed 1 drink per day
- **Drug abuse**
 - Most commonly associated: cocaine, amphetamines, and heroin
 - Strokes in this group are often seen in a younger population

Stroke - RISK FACTORS

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**

Stroke - RISK FACTORS

- **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**

Stroke - RISK FACTORS

- **American Stroke Association ²**



Image from StrokeAssociation.org (3/13/2013)

Stroke

Two Types

Stroke - TWO TYPES

First, a couple of definitions:

- **Infarct:** Area of necrosis resulting from a sudden insufficiency of blood supply ⁶
- **Ischemia:** Mechanical obstruction of blood supply resulting in organ dysfunction ⁶

Stroke - TWO TYPES

First, a couple of definitions:

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

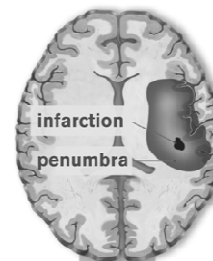


Image from Activase.com (3/14/2013)

Stroke - TWO TYPES

1) Ischemic Stroke

- **A clot obstructs the flow of blood to the brain ²**
- **Accounts for 87% of all strokes ^{2,3}**

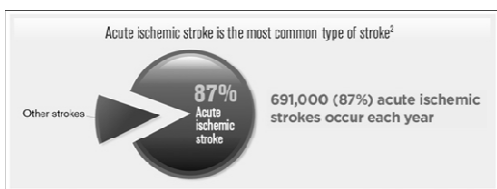


Image from Activase.com (3/14/2013)

Stroke - TWO TYPES

1) Ischemic Stroke ²

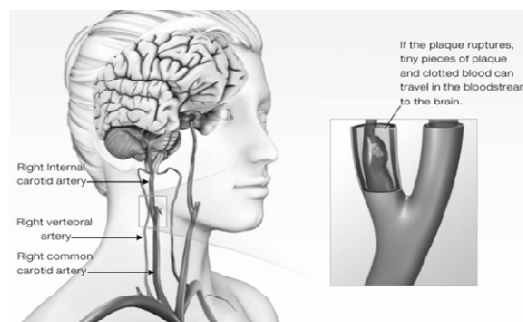


Image from StrokeAssociation.org (3/13/2013)

Stroke - TWO TYPES

1) Ischemic Stroke ²

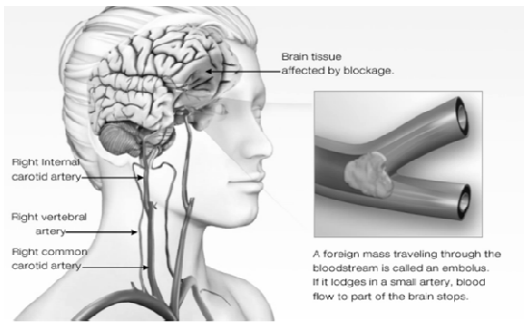


Image from StrokeAssociation.org (3/13/2013)

Stroke - TWO TYPES

Transient Ischemic Attack (TIA) ²

- 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

Stroke - TWO TYPES

2) Hemorrhagic Stroke

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

Stroke - TWO TYPES

2) Hemorrhagic Stroke ²

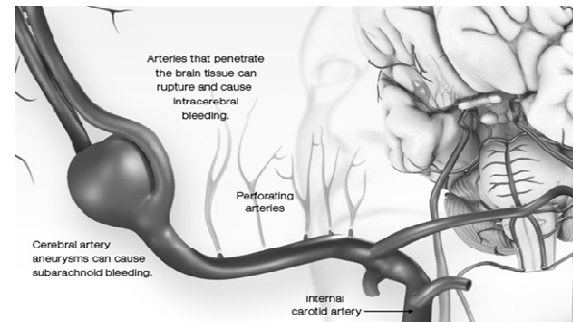


Image from StrokeAssociation.org (3/13/2013)

Stroke - TWO TYPES

2) Hemorrhagic Stroke – ICH ²

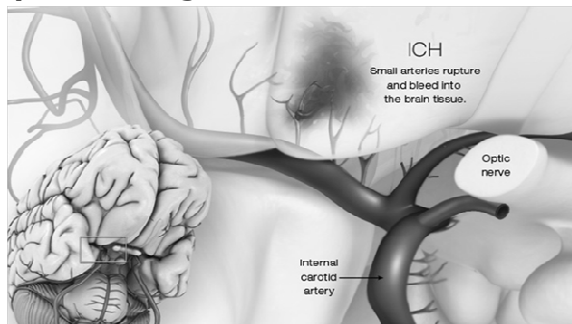


Image from StrokeAssociation.org (3/13/2013)

Stroke - TWO TYPES

2) Hemorrhagic Stroke – SAH ²

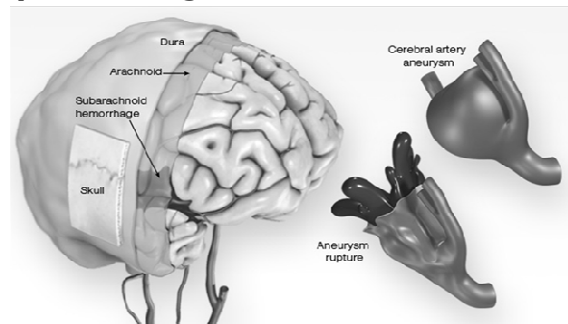


Image from StrokeAssociation.org (3/13/2013)

Stroke - TWO TYPES

Other ailments that may appear stroke-like include: ⁷

- 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

Stroke - TWO TYPES

Why is the cause of the stroke symptoms important?

Treatment depends on what caused the stroke

Alteplase (recombinant tPA)

Alteplase (recombinant tPA)

Brand Names

- Activase®
- Cathflo® Activase®

Name confusion

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

No generic alternatives available

Alteplase (recombinant tPA)

Pharmacologic class:
Thrombolytic agent

Mechanism of action: ⁶
Initiates local fibrinolysis by binding to fibrin in a thrombus (clot) and converts entrapped plasminogen to plasmin

Alteplase (recombinant tPA)

Pharmacodynamics / Pharmacokinetics ⁶

- **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: ⁶ None

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 (recombinant tPA)

Alteplase is produced by recombinant DNA technology

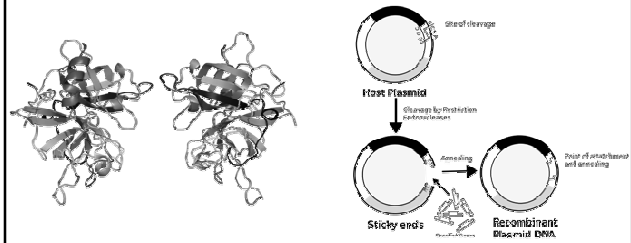


Image from en.wikipedia.org/wiki/Tissue_plasminogen_activator (3/15/2013)

Image from en.wikipedia.org/wiki/Recombinant_DNA (3/15/2013)

Alteplase for Stroke

Ischemic Strokes

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

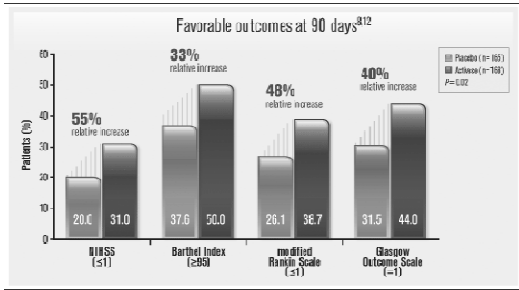
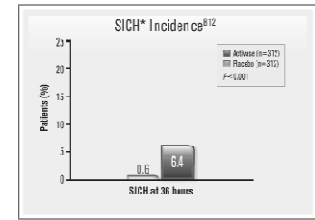
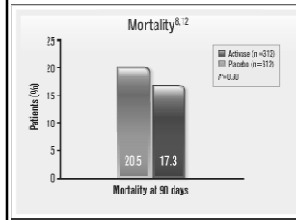


Image from Activase.com (3/14/2013)

Alteplase for Stroke - ISCHEMIC STROKES

- When alteplase was given within 3 hours of last known normal: 8
- Mortality at 3 months: No Difference



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

Alteplase for Stroke

Window of Time

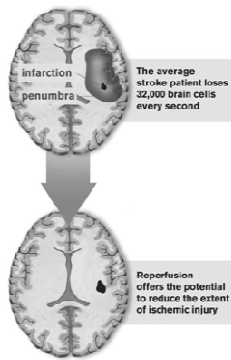
Alteplase for Stroke - WINDOW OF TIME

Estimated pace of neurologic loss in a typical large-vessel acute ischemic stroke¹⁰

	Neurons	Accelerated aging
Every second	32,000	8.7 hours
Every minute	1.9 million	3.1 weeks
Every hour	120 million	8.6 years
10 hours*	1.2 billion	36 years

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

Alteplase for Stroke - WINDOW OF TIME



10

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

Alteplase for Stroke - WINDOW OF TIME

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

Alteplase for Stroke - WINDOW OF TIME

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

Alteplase for Stroke - WINDOW OF TIME

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

Alteplase for Stroke - WINDOW OF TIME

Meeting the time requirement can be a challenge:

– Once at the hospital:



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

Alteplase for Stroke

Precautions

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

Alteplase for Stroke - PRECAUTIONS

Contraindications for use in ischemic stroke: ⁶

- 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 \leq 1.7)
 - INR > 1.7 (or PT > 15 seconds)
 - Administration of heparin in last 48 hours WITH elevated aPTT
 - Platelet count < 100,000/mm³

Alteplase for Stroke - PRECAUTIONS

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: ⁶**

- 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

Alteplase for Stroke - PRECAUTIONS**When administered, must monitor: ⁶**

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

Alteplase for Stroke - PRECAUTIONS**Adverse reactions that occur 1 to 10% of the time: ⁶**

- 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%)

Alteplase for Stroke - PRECAUTIONS**Other significant adverse reactions: ⁶**

- Cerebral edema
- Cerebral herniation
- Seizure
- New ischemic stroke

Preparation of Alteplase

Preparation of Alteplase

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)



Preparation of Alteplase

Reconstitution: ^{6,9}

– Mix by gently swirling or slow inversion – Avoid agitation

- Not compatible with preservatives or D5W ¹⁷

– Solution should be:

- Transparent
- Clear or pale yellow

– Final concentration: 1 mg/mL

Preparation of Alteplase

Reconstitution: ^{6,9}

– Use within 8 hours

– Can freeze (–20 °C) and store for up to 6 months ¹⁷

– Do not shake ^{6,9} or send through tube system

Preparation of Alteplase

Dose for acute ischemic stroke ⁶

- **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: ⁶

- **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

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

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

1. KochanekKD, Xu J, Murphy SL, *et al.* Deaths: Preliminary Data for 2009. *Natl Vital Stat Rep* 2011; 59: 1.
2. American Stroke Association website: www.strokeassociation.org Accessed 13 March 2013.
3. Roger VL, Go AS, Lloyd-Jones DM, *et al.* Heart disease and stroke statistics – 2011 update: a report from the American Heart Association. *Circulation* 2011; 123: e18.
4. Solomon NA, Glick HA, Russo CJ, *et al.* Patient preferences for stroke outcomes. *Stroke* 1994; 25: 1721.
5. Kothari RU, Pancioli A, Liu T, Broderick J, Cincinnati Prehospital Stroke Scale: reproducibility and validity. *Ann Emerg Med* 1999; 33(4): 373.
6. Lexi-Comp, Inc. (Lexi-Drugs). Lexi-Comp, Inc.; version 1.11.0(160): 13 March 2013.
7. Caplan LR. Differential diagnosis of transient ischemic attack and stroke. In: *UpToDate*, Kasner SE (Ed), *UpToDate*, Waltham, MA, 2013.
8. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995; 333: 1581.
9. Activase® [package insert]. South San Francisco, CA: Genentech, Inc.; 2011.
10. Saver JL. Time is brain-quantified. *Stroke* 2006; 37: 263.

References

11. Marler JR, Tilley BC, Lu M, *et al*. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology* 2000; 55: 1649.
12. Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; 359: 1317.
13. IST-3 collaborative group, Sandercock P, Wardlaw JM, *et al*. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet* 2012; 379: 2352.
14. Wardlaw JM, Murray V, Berge E, *et al*. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet* 2012; 379: 2364.
15. Lees KR, Bluhmki E, von Kummer R, *et al*. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010; 375: 1695.
16. Kleindorfer D, Kissela B, Schneider A, *et al*. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke: a population-based study. *Stroke* 2004; 35: e27.
17. Alteplase (t-PA) AHFS 20:12.20. In: *Handbook of Injectable Drugs*, 15th Edition, Trissel LA (Ed), American Society of Health-System Pharmacists, Bethesda, MD, 2008.