**Stroke Pharmacotherapy**

Monique Calil, Pharm.D.
PGY-1 Pharmacy Resident
Broward Health Medical Center

www.fshp.org

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**Disclosure**

“I have no relevant financial relationships or commercial interests to disclose in conjunction with this presentation.”

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**Objectives**

**Pharmacists**

- Review the definitions, epidemiology, and risk factors for stroke
- Determine eligibility for thrombolytic medications using patient-specific factors in ischemic stroke and what the available options are
- Assess how to manage blood pressure in patients with acute ischemic stroke
- Summarize how to prevent complications associated with ischemic stroke

**Technicians**

- Evaluate the definitions, epidemiology, and risk factors for stroke
- Outline how to calculate the dose and prepare the thrombolytic alteplase (Activase®) for administration
- Review how to prevent complications associated with ischemic stroke
Definitions: Stroke

- **Ischemic** (85%): neurological dysfunction caused by focal, spinal, or retinal infarction
  - Cardioembolic
  - Non-Cardioembolic
- **Hemorrhagic** (15%): neurological dysfunction caused by bleeding
  - Intracerebral
  - Subarachnoid
- **Transient Ischemic Attack (TIA)**: neurological dysfunction caused by focal or retinal ischemia
  - “Mini-stroke”
  - Different definitions; Symptoms typically last for < 1 hour
  - No infarction

Pathophysiology of Ischemic Stroke

- Thromboembolic disease → Vascular occlusion → Ischemia
  - No energy (↓ ATP) to maintain ionic gradients → influx Ca²⁺ and Na⁺ → Edema
  - ↑ Glutamate → ↑ NMDA = excitatory depolarization = More influx Ca²⁺
  - ↑ Glutamate and ↑ ischemia
- Degradative enzymes from ↑ ↑ ↑ Ca²⁺ = destruction of cell membrane and neuronal structures
- Free radicals, arachidonic acid, and nitric oxide are generated
  → Further neuronal damage
- Core ischemic area versus ischemic penumbra

Epidemiology

- Stroke is the 4th leading cause of death in the U.S.
- 795,000 people in the U.S. experience new (610,000 people) or recurrent (185,000 people) stroke
- ~85% of strokes reported in the U.S. are ischemic
- 74% of all strokes occur in those > 64 years old

Risk Factors for Ischemic Stroke

**Non-modifiable risk factors**
- Age
- Race
- Sex
- Ethnicity
- History of migraine headaches
- Fibromuscular dysplasia
- Heredity

**Modifiable risk factors**
- Hypertension
- Diabetes Mellitus
- Cardiac disease
- Hypercholesterolemia
- TIA’s
- Carotid stenosis
- Hyperhomocystinemia
- Excessive alcohol intake, tobacco use, illicit drug use, physical inactivity
- Obesity
- Oral contraceptive use
- Sickle cell disease
### Differential Diagnosis

<table>
<thead>
<tr>
<th>Disease states</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychogenic</td>
<td>No objective cranial nerve findings, neurological findings in a nonvascular distribution, inconsistent exam</td>
</tr>
<tr>
<td>Seizures</td>
<td>Hx of seizures, witnessed seizure activity, postictal period</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Hx of DM, ↓ glucose, ↓ level of consciousness</td>
</tr>
<tr>
<td>Migraine w/ aura</td>
<td>Hx of similar events, preceding aura, headache</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>Headache, delirium, significant HTN, cortical blindness, cerebral edema, seizure</td>
</tr>
<tr>
<td>Wernicke’s encephalopathy</td>
<td>Hx of alcohol abuse, ataxia, ophthalmoplegia, confusion</td>
</tr>
<tr>
<td>CNS abscess</td>
<td>Hx of drug abuse, endocarditis, medical device implant w/ fever</td>
</tr>
<tr>
<td>CNS tumor</td>
<td>Gradual progression of 1st, other 1st malignancy, seizure at onset</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>Lithium, phenytoin, carbamazepine</td>
</tr>
</tbody>
</table>

### Diagnosis

#### National Institute of Health Stroke Scale (NIHSS)

- **↑ Score = ↑ Stroke severity**
- **< 4 = higher likeliness of good clinical outcomes**
- **> 22 = higher association with intracranial hemorrhage after fibrinolytics**

### Goals of Therapy

- **Reperfusion !!!!!**
- Prevent further ischemia in cerebral tissue
- Decrease signs/symptoms of neurological dysfunction
- Improve final functional outcome through reperfusion
- Minimize adverse effects

### Emergent brain imaging (≤ 25 minutes)

- Non-enhanced CT (NECT) or MRI
  - To rule out contraindications to fibrinolytic therapy
  - Early ischemic changes
  - Frank hypodensity

### Labs

- **Blood glucose**
- **O2 saturation**
- **Serum electrolytes**
- **Renal function tests**
- **CBC**
- **PTT/INR**
- **aPTT**
- **ECG**
- **Markers of cardiac ischemia**
Treatment of Acute Complications

- Hyperthermia
  - Poor neurological outcomes
  - Goal: achieve normothermia
- Hyperglycemia
  - Worse clinical outcome
  - Goal: Blood Glucose 140-180 mg/dL
- Arterial Hypertension
  - Spontaneous Intracerebral Hemorrhage (sICH)
  - Goal: < 185/110 mmHg

AHA/ASA Recommendations:

- Treatment **with** fibrinolytics:
  - Goal: < 185/110 mmHg
  - Risk of spontaneous intracerebral hemorrhage (sICH)
- **No** fibrinolytics:
  - Goal: < 220/120 mmHg
  - BP goal not well-defined

Acute Treatment of Ischemic Stroke: Arterial Hypertension

Eligible for acute reperfusion tx, but BP is > 185/110 mmHg

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>10-20 mg IV 1-2 minutes, may repeat x 1</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>5 mg/hr, then IV infusion 2.5 mg/min</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Hydralazine, enalapril</td>
<td></td>
</tr>
</tbody>
</table>

Management of BP during/after acute reperfusion tx for goal < 180/105 mmHg

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</table>

Not controlled/diastolic BP > 140 mmHg

<table>
<thead>
<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>IV sodium nitroprusside</td>
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Fibrinolytic Agents

- **Streptokinase (Streptase®)** – No longer available in the U.S.
- **Urokinase (Abbokinase®)** – No longer available in the U.S.
- **Tenecteplase (TNKase®)** – Myocardial infarction
- **Reteplase (Retavase®)** – Myocardial infarction
- **Alteplase (Activase®)** – Acute ischemic stroke, Pulmonary Embolism (PE), Myocardial Infarction (MI)

Alteplase (Activase®)

**Mechanism of action:**
- Recombinant tissue plasminogen activator (rt-PA)
- Binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin, initiating local fibrinolysis with limited systemic proteolysis

**Dosing:**
- Total: IV 0.9 mg/kg (Max is 90 mg)
  - 10% of total dose as IV bolus over 1 minute (Max 9 mg)
  - 90% of total dose as IV infusion over 60 minutes (Max 81 mg)

**Duration:**
- ~80% cleared in 10 minutes
- Fibrinolytic activity persists for up to 1 hour after infusion

**Adverse drug reactions:**
- Intracranial hemorrhage – 6.4-7.9%
- Hypotension
- Fever
- Angioedema (1.3-5.1%)
- Allergic reactions

**Monitor:**
- Head CT, CBC, aPTT, PT/INR, glucose
- Neurological assessment
  - Q15 min during infusion, Q30 minutes x 6 hours, Q1hr x 18 hours
- Blood pressure
  - Q30 minutes x 2 hrs, Q2hr minutes x 6 hours, Q1 hr x 18 hours
  - [Goal < 180/105 mmHg]
- Head CT follow up 24 hours after treatment
IV Fibrinolytic therapy: Timing

Within 3 hours of onset of ischemic stroke
- Recommendation from AHA/ASA; Class I, Evidence A
- Results from 1995 NINDS Trial

Within 3-4.5 hours of onset of ischemic stroke
- Recommendation from AHA/ASA; Class I, Evidence B
- Results from 2008 ECASS III Trial
- Additional exclusion criteria
- Not FDA-approved

Within 4.5-6 hours of onset of ischemic stroke
- Not recommended from AHA/ASA
- Controversial


IV Fibrinolytic therapy: Criteria within 3 hours

**Inclusion Criteria**
- Ischemic stroke w/ measurable neurological deficit
- Onset of Symptoms < 3 hrs
- Age ≥ 18 YO


**Exclusion Criteria**
- Significant head trauma or prior stroke in previous 3 months
- Se of subarachnoid hemorrhage
- Arterial puncture at noncompressible site in previous 7 days
- He of previous intracranial hemorrhage
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Recent intracranial or intraspinal surgery
- Elevated BP: Systolic > 185 or diastolic > 110 mmHg
- CT with multilobar infarction (hypodensity > 1/3 cerebral hemisphere)


Weigh Risks versus Benefits

**Relative Exclusion Criteria**
- Only minor or rapidly improving stroke symptoms (clearing spontaneously)
- Pregnancy
- Seizure at onset with postictal residual neurological impairments
- Major surgery or serious trauma within previous 14 days
- Recent GI or urinary tract hemorrhage (within previous 21 days)
- Recent acute MI (within previous 3 months)

**IV Fibrinolytic therapy:**
Criteria within 3 to 4.5 hours

**Additional Inclusion and Exclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Relative Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of ischemic stroke with measurable neurological deficit</td>
<td>Aged &gt; 80 YO</td>
</tr>
<tr>
<td>Onset of symptoms within 3-4.5 hours</td>
<td>Severe stroke (NIHSS &gt; 25)</td>
</tr>
<tr>
<td></td>
<td>Taking an oral anticoagulant regardless of INR</td>
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<tr>
<td></td>
<td>Hx of both diabetes mellitus (DM) and prior ischemic stroke</td>
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**Alteplase (Activase®)**

**Reconstituting alteplase (Activase):**
1. Insert piercing pin into sterile water for injection (SWFI) vial
2. Push vial of Activase® own into transfer device through center of Activase® vial stopper
3. Invert the two vials: Activase® vial at the bottom, SWFI vial on top
4. Allow the entire contents of the vial of SWFI to flow down through the transfer device into the vial containing Activase®; ~0.5 mL will remain in SWFI vial
5. Gently, swirl Activase® vial. Do not shake!
6. Let solution stand for a few minutes
7. Solution is a colorless to pale, yellow and transparent
8. Concentration is now 1 mg/mL

**Preparing dose of alteplase (Activase):**
1. Discard excess quantity from the vial
   - Insert needle away from puncture site made by transfer device
   - Remainder left inside Activase® vial should be total mL for patient
2. Bolus dose is 10% of the 0.9 mg/kg total dose
   - Remember: Concentration is 1 mg/2 mL
   - Remove this dose in mL from the vial by inserting needle away from puncture site made by transfer device
3. Preparing infusion set: remainder mL in vial
   - 100 mg vial
     - The vial itself with remainder drug can be used with an infusion set (it has a clear plastic hanger from vial label)
     - Can be drawn up and inserted into polyvinyl chloride (PVC) bag
     - 50 mg vial
       - Draw up and insert into a PVC or glass vial and infusion set
Alteplase (Activase®)

Pearls about reconstituting alteplase (Activase):
• Reconstituted vial is stable for up to 8 hrs in room temperature
  – Does not contain antimicrobial preservatives
• Dosing and administration differs from other indications such as pulmonary embolism (PE) and myocardial infarction (MI)
• To ensure full dose is delivered:
  – Spike a small bag (eg, 50 mL) of 0.9% Sodium Chloride, USP, with end of the Activase® infusion set when the Activase® vial is empty
  – The infusion should continue at the same rate

Intra-arterial Fibrinolysis
• Currently, no FDA-approved drug for intra-arterial use
• 2 randomized trials show benefit: PROACT II (1999) and MELT (2007)
  • Recombinant pro-urokinase, within 6 hours (PROACT II)
  • Urokinase, within 6 hours (MELT)
• May be more efficacious:
  • For proximal arterial occlusions, larger thrombi
  • For those with severe neurological deficits (NIHSS score ≥ 10)
  • For treatment within 6 hours
• Dose?
  – Optimal dose unknown
  – Some studies used ~22 mg total dose

Fibrinolytic therapy: Timing

Intra-arterial Fibrinolysis
AHA/ASA Recommendations
• “…beneficial for treatment of carefully selected patients with major ischemic strokes < 6 hours’ duration caused by occlusions of the middle cerebral artery who are not otherwise candidates for IV rt-PA”
  – Class I; Level of Evidence B
• Thrombectomy devices can be useful in achieving recanalization alone or in combination with pharmacological fibrinolysis in carefully selected patients
  – Class IIa; Level of Evidence B
• Rescue intra-arterial fibrinolysis or mechanical thrombectomy may be reasonable approaches to recanalization in patients with large artery occlusion who have not responded to IV fibrinolysis
  – Class IIIb; Level of Evidence B

Anticoagulants
- Thought to lessen risk of neurological worsening
  - Mixed results
- Risk of pulmonary embolism (PE) and deep vein thrombosis
  (DVT) remains
  - PREVAIL Study
    • Enoxaparin 40 mg daily more effective than heparin 5,000 units every 12 hours in preventing venous thromboembolism (VTE) (10% versus 18%)
- Administration of anticoagulants within 24 hours after treatment with IV rt-PA is contraindicated
  - Based on clinical trial protocol in the NINDS trials

Antiplatelets
- Demonstrated reduction in early recurrent stroke
  - Most studies are with aspirin
  - Benefit with clopidogrel is not well established
  - Not clear if antiplatelets also limit neurological consequences
- Oral administration of aspirin 325 mg within 24-48 hours after stroke onset is recommended
- Administration of antiplatelets within 24 hours of IV fibrinolysis is not recommended
  - Study by Zinkstok, et. al.
    • IV aspirin within 90 minutes of IV rtPA versus IV rtPA alone
    • Stopped early due to ↑↑ intracranial hemorrhage

Secondary Prevention
- Antiplatelet therapy
- Anti-hypertensive therapy
- Lipid management
- Diabetes screening
Secondary Prevention

Antiplatelet therapy
- Antiplatelets rather than oral anticoagulation
  - To reduce risk of recurrent stroke and other cardiovascular events for non-cardioembolic stroke or TIA
- Agents:
  - Aspirin 50-325 mg daily (Class I; Level of Evidence A)
  - Aspirin 25 mg and extended-release dipyridamole 200 mg BID (Class I; Level of Evidence B)
  - Clopidogrel 75 mg daily (Class IIa; Level of Evidence B)

Secondary Prevention

Lipid management
- Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events in ischemic stroke or TIA:
  - With LDL-C ≥ 100 mg/dL (Class I; Level of Evidence B)
  - With LDL-C < 100 mg/dL (Class I; Level of Evidence C)
- High-intensity statin
  - Lowers LDL-C by ≥ 50%
  - Atorvastatin 40-80 mg daily
  - Rosuvastatin 20-40 mg daily

Secondary Prevention

Antihypertensive therapy
- Blood pressure (BP) reduction recommended for prevention of recurrent stroke and other vascular events
- For systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg that persists "beyond the first several days"
  - Optimal target BP not established
- Optimal drug regimen is uncertain
  - Diuretics +/- ACE-inhibitors

Secondary Prevention

Diabetes screening
- Up to 28% of patients with ischemic stroke have pre-diabetes mellitus (DM)
- 25% to 45% have overt DM
- Recommendation:
  - After a TIA or ischemic stroke, all patients should probably be screened for DM with testing
    - Fasting plasma glucose
    - HbA1c, or
    - Oral glucose tolerance test
Patient Education

- Good outcomes start with recognition
- < 50% of 9-1-1 calls for stroke made within 1 hr of Sx
- Stroke recognition
  - Fibrinolytic treatment could be increased from 4.3% to 28.6% if all patients arrived early after onset
- Emergency Medical Services (EMS) Transport
  - 53% of stroke patients used EMS
- F-A-S-T
  - 88% of all strokes or TIAs have ≥ 1 of these

EDUCATION IS KEY!!!

Stroke Certification Programs

<table>
<thead>
<tr>
<th>Program Concept</th>
<th>Acute Stroke Ready Hospital (ASRH)</th>
<th>Primary Stroke Center (PSC)</th>
<th>Comprehensive Stroke Center (CSC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Stroke team</td>
<td>24/7</td>
<td>24/7</td>
<td>24/7</td>
</tr>
<tr>
<td>Stroke Unit</td>
<td>No designated beds</td>
<td>Stroke unit/designated beds</td>
<td>Neuro ICU</td>
</tr>
<tr>
<td>Neurosurgical Services</td>
<td>Within 3 hours (transfer)</td>
<td>Within 2 hours</td>
<td>24/7</td>
</tr>
<tr>
<td>Treatment capabilities</td>
<td>IV thrombolytics</td>
<td>IV thrombolytics plus some neurointerventions</td>
<td>IV thrombolytics plus all neurointerventions</td>
</tr>
</tbody>
</table>

http://www.cdc.gov/pcd/issues/2008/apr/07_0214.htm

Patient Education

http://www.cdc.gov/pcd/issues/2008/apr/07_0214.htm

Primary Stroke Centers Certification

The Joint Commission
- Broward Health Medical Center
- Broward Health Coral Springs
- Broward Health Imperial Point
- Holy Cross Hospital
- Broward Health North
- Northwest Medical Center
- Kendall Regional Medical Center
- Memorial Hospital Pembroke
- Memorial Hospital West
- Miami Beach HealthCare Group
- University of Miami Hospital
- Jackson Memorial Hospital
- Jackson North Medical Center
- Hialeah Hospital
- Palmetto General Hospital
- Mount Sinai Medical Center of FL
- Memorial Regional Hospital
- Cleveland Clinic Florida

Florida Agency of Healthcare Administration
- Plantation General Hospital
- Mercy Hospital
- Tenet Health System North Shore

http://www.jointcommission.org/assets/1/18/StrokeProgramGrid_abbr_AHA-TJC_5-1-15.pdf

http://www.qualitycheck.org/consumer/SearchQCR.aspx

http://www.floridaonclick.com

http://www.ahca.myflorida.com

http://www.qualitycheck.org/consumer/SearchQCR.aspx

https://ahca.myflorida.com

https://www.qualitycheck.org/consumer/SearchQCR.aspx
Comprehensive Stroke Centers Certification

The Joint Commission:
- Baptist Hospital of Miami

Florida Agency of Healthcare Administration
- Broward Health Medical Center
- Westside Regional Medical Center
- Kendall Regional Medical Center
- Florida Medical Center
- Holy Cross Hospital
- Jackson Memorial Hospital
- Palmetto General Hospital
- Bakers Hospital
- Mount Sinai Medical Center of FL
- Memorial Regional Hospital
- Memorial Hospital West
- Cleveland Clinic Hospital
- Adventura Hospital and Medical Center
- Baptist Hospital of Miami

Conclusion

- Stroke is a serious medical emergency that needs to be recognized and treated in a timely manner...Time is Brain!
- Fibrinolytic therapy with the rt-PA alteplase (Activase®) remains to be the first line treatment option for patients with ischemic stroke
- Recognizing criteria for use including blood pressure is critical to initiate or withhold treatment with fibrinolytic therapy
- Pharmacists and technicians play an integral role in the treatment of patients with ischemic stroke

Assessment Questions: True/False

- The difference between stroke and transient ischemic attack (TIA) is that a TIA is less serious and symptoms typically last < 10 hours
  - False
- The IV thrombolytic rt-PA should be administered within 3 hours from the time the patient presents to the hospital
  - False
- In order for eligible patients to receive IV rt-PA, their blood pressure must be maintained < 185/110 mmHg for 24 hours
  - False

References

- Introduction slide image: http://www.webmd.com/stroke/
## References