Thrombolytic Therapy of Acute Stroke

Steven K. Feske, MD

Case 1. A 65-year-old right-handed man with no history of heart disease presented to the emergency department with right-sided weakness and an inability to speak. His wife last saw him well 1 hour before his arrival. His ECG showed atrial fibrillation with a ventricular response of 100 bpm; his blood pressure was 175/88 mm Hg. He was alert, but he did not produce or comprehend speech. He did not blink to a threat presented in the right visual field. There was weakness of the right lower face and of the right arm and leg (National Institutes of Health Stroke Scale score, 15 of a possible 42). A noncontrast cranial computed tomography (CT) image showed no hemorrhage and no signs of early ischemia.

Case 2. A 39-year-old woman in good general health was found mumbling incoherently with left-sided weakness. She had been well minutes before. She was brought to a local hospital where she was noted to neglect her left personal space and to have left homonymous hemianopsia, rightward eye deviation, left lower facial weakness, and left arm and leg weakness (National Institutes of Health Stroke Scale score, 17). A head CT showed no hemorrhage or early ischemia, and she was given intravenous tissue-type plasminogen activator (tPA) before transfer to a comprehensive stroke center for consideration of intra-arterial therapy. On arrival at the receiving facility shortly after completion of the tPA infusion, her examination had not improved. A noncontrast head CT showed some loss of gray-white differentiation in the right parietal lobe (Figure 1A) and posterior insular cortex, and a CT angiogram showed abrupt cutoff of the right middle cerebral artery stem (Figure 1B). A conventional angiogram confirmed the right middle cerebral artery stem occlusion (Figure 1C).

The therapy of acute stroke has advanced dramatically over the last 15 years with the use of intravenous tPA and intra-arterial catheter-based revascularization techniques. At their best, these therapies allow the physician to arrest the progression of what would otherwise become a devastating stroke. Yet, the majority of patients with stroke still do not benefit from these therapies either because the brief time window of benefit and safety imposes administrative, medical, and logistical demands that have not been met or because, even when applied early, these therapies are effective in only some patients. Therefore, it is important that we expand access to and implement currently available therapies as efficiently as possible. In addition, we must continue to refine these therapies and to develop new ones. This review provides a focused update on the current therapy of acute stroke.

Challenges to the Implementation of Thrombolytic Therapy for Stroke

The great majority of ischemic strokes are due to cerebral arterial occlusion by thrombus, providing a straightforward rationale for the use of thrombolytic medications. Experience with acute myocardial infarction, pulmonary embolism, and other thrombotic diseases provides clinical precedents that also predict success for stroke. However, many obstacles to the optimal implementation of thrombolytic therapy for stroke remain. The need to act very rapidly to promote clot lysis before the infarct size is great and the resistance of many thrombi to pharmacological lysis based on differences in the size, age, degree of retraction, platelet-fibrin versus erythrocyte-rich composition, and levels of plasminogen activator inhib-
itor represent logistical and biological limitations and challenges.\(^1,2\) The relative susceptibility of the brain to hemorrhage,\(^3\) the variability of symptoms and signs of stroke that are confusing to both patients and clinicians, and the lack of urgency that many patients display in seeking medical care after the onset of stroke symptoms also limit therapy for acute stroke compared with myocardial infarction. Therefore, to implement thrombolytic therapies for stroke effectively, we must consider and address both biological and system-level obstacles.

### Intravenous Thrombolysis

Published in December 1995, the National Institute of Neurological Disorders and Stroke (NINDS) trial of tPA was the first large randomized controlled trial to show a benefit of thrombolysis for acute ischemic stroke.\(^4\) Patients with moderate to severe stroke and no evidence of hemorrhage on cranial CT were given intravenous tPA within 3 hours of symptom onset. Blood pressure was then managed strictly by protocol for 24 hours to avoid excessive elevation (Table 1).\(^5\) Treated patients were 50%

---

**Table 1. Management of Hypertension in Acute Ischemic Stroke**

<table>
<thead>
<tr>
<th>BP level</th>
<th>Indication that patient is eligible for treatment with intravenous tPA or other acute reperfusion intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic &gt;185 mm Hg or diastolic &gt;110 mm Hg</td>
<td>Labetalol 10–20 mg IV over 1–2 min, may repeat 1 time; or Nitroglycerin paste 1–2 in; or Nicardipine infusion 5 mg/h, titrate up by 0.25 mg/h at 5- to 15-min intervals, maximum dose 15 mg/h; when desired BP is attained, reduce to 3 mg/h</td>
</tr>
<tr>
<td>If BP does not decline and remains &gt;185/110 mm Hg, do not administer tPA</td>
<td></td>
</tr>
</tbody>
</table>

Management of BP during and after treatment with tPA or other acute reperfusion intervention

- Monitor BP every 15 min during treatment, then for another 2 h, then every 30 min for 6 h, and then every hour for 16 h
- Blood pressure level
  - Systolic 180–230 mm Hg or diastolic 105–120 mm Hg: Labetalol 10 mg IV over 1–2 min, may repeat every 10–20 min, maximum dose 300 mg; or Labetalol 10 mg IV followed by an infusion at 2–8 mg/min
  - Systolic >230 mm Hg or diastolic 121–140 mm Hg: Labetalol 10 mg IV over 1–2 min, may repeat every 10–20 min, maximum dose 300 mg; or Labetalol 10 mg IV followed by an infusion at 2–8 mg/min; or Nicardipine infusion 5 mg/h, titrate up to desired effect by increasing 2.5 mg/h every 5 min to maximum of 15 mg/h
  - If BP remains uncontrolled, consider sodium nitroprusside

---

IPA indicates tissue-type plasminogen activator; BP, blood pressure.

Adapted from Adams et al.\(^5\)

(relative increase; 13% absolute) more likely to achieve a recovery with no significant disability after 3 months (part 2, modified Rankin Scale score outcome). This benefit was achieved at the cost of a 10-fold increase in the rate of symptomatic intracranial hemorrhage (6% versus 0.6%). However, this increase did not result in a higher rate of death or severe disability in the
### Table 2. Inclusion and Exclusion Criteria for Intravenous Tissue-Type Plasminogen Activator in Patients With Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of ischemic stroke causing measurable neurologic deficit</td>
<td>Head trauma or prior stroke within the previous 3 mo</td>
</tr>
<tr>
<td>Onset of symptoms &lt;3 h before start of treatment (or, in selected cases, &lt;4.5 h)</td>
<td>Symptoms suggestive of subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Age ≥18 y</td>
<td>Arterial puncture at noncompressible site within the previous 7 d</td>
</tr>
<tr>
<td></td>
<td>History of intracranial hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Elevated blood pressure (systolic ≥185 mm Hg or diastolic ≥110 mm Hg) that has not responded to antihypertensive treatment</td>
</tr>
<tr>
<td></td>
<td>Evidence of active bleeding on examination</td>
</tr>
<tr>
<td></td>
<td>Acute bleeding diathesis, including but not limited to the following</td>
</tr>
<tr>
<td></td>
<td>Platelet count ≥100 000/mm³</td>
</tr>
<tr>
<td></td>
<td>Heparin received within 48 h, resulting in aPTT at or above the upper limit of normal</td>
</tr>
<tr>
<td></td>
<td>Current use of anticoagulant, with INR ≥1.7 or PT ≥15 s</td>
</tr>
<tr>
<td></td>
<td>Blood glucose concentration ≥50 mg/dL (2.7 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>CT evidence of multilobar infarction (hypodensity more than one third of the cerebral hemisphere)</td>
</tr>
<tr>
<td></td>
<td>Relative exclusion criteria, depending on risk-to-benefit ratio†</td>
</tr>
<tr>
<td></td>
<td>Only minor or rapidly improving stroke symptoms (clearing spontaneously)</td>
</tr>
<tr>
<td></td>
<td>Seizure at onset with postictal residual neurologic impairments</td>
</tr>
<tr>
<td></td>
<td>Major surgery or serious trauma within the previous 14 d</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal or urinary tract hemorrhage within the previous 21 d</td>
</tr>
<tr>
<td></td>
<td>Acute myocardial infarction within the previous 3 mo</td>
</tr>
</tbody>
</table>

*Criteria for extension of the time window to 4.5 hours are based on the results of the European Cooperative Acute Stroke Study III (ECASS III) in which the following more selective criteria were added: age >80 years, severe stroke defined by National Institutes of Health Stroke Scale score ≥25, current anticoagulant therapy regardless of INR, and history of both diabetes mellitus and past stroke.

Recent experience suggests that under some circumstances, with careful consideration and weighing of the risks versus benefits of tissue-type plasminogen activator administration, patients may receive thrombolytic therapy despite 1 or more of the listed relative contraindications.

Reprinted from Wechsler6 with permission of the publisher. © Copyright 2011, Massachusetts Medical Society.

treated group. On the basis of the findings of this study, tPA (0.9 mg/kg; maximum, 90 mg) was licensed by the Food and Drug Administration in June 1996 for use within 3 hours of the onset of ischemic stroke. Eligibility criteria for tPA are shown in Table 2.6

Initial use of intravenous tPA was limited to the <3-hour time window established in the NINDS trial. However, a meta-analysis of data from this and other studies with time windows up to 6 hours suggested that intravenous tPA could be given with significant but decreasing benefit and an acceptable risk-to-benefit ratio up to 4.5 hours.7 The extension of the window for the use of intravenous tPA was tested in a randomized, controlled trial published in 2008 that confirmed the findings of the prior meta-analysis. In the European Cooperative Acute Stroke Study III (ECASS III), patients with some exclusion criteria added to those imposed in the NINDS study (Table 2) were treated with intravenous tPA within 4.5 hours.8 Treated patients were 16% (relative increase; 7.2% absolute) more likely to achieve a recovery with no significant disability after 3 months. As in the NINDS trial, treatment was associated with a higher risk of symptomatic intracranial hemorrhage. However, this did not result in a higher rate of death or severe disability. Extension of the therapeutic window for intravenous tPA for acute stroke has been endorsed by the American Stroke Association and included in its guidelines, and this policy has been adopted by many stroke centers. However, the Food and Drug Administration has not licensed tPA for this extended use.9

Imaging studies of stroke indicate that areas of ischemic brain that render patients severely symptomatic progress over many hours, gradually incorporating tissue peripheral to the ischemic center.10 Such areas of hypoperfused yet viable brain can be detected with a useful practical degree of accuracy by advanced magnetic resonance and CT imaging, with mismatch measured as a large perfusion deficit that is not yet matched by a large infarct as defined by areas of diffusion restriction on magnetic resonance imaging or areas of decreased cerebral blood volume on perfusion magnetic resonance or CT (Figure 2). It is an attractive but as yet unproven hypothesis that such imaging will allow the selection of patients who might benefit from thrombolytic treatment well after the currently accepted time windows. Although some promising preliminary results support the validity of this approach, early attempts to confirm its benefit in clinical trials have not yet succeeded.11

**Intra-Arterial Thrombolysis**

Off-label use of streptokinase and urokinase preceded intravenous tPA in clinical practice for selected high-risk strokes. In 1999, intra-arterial prourokinase given, without mechanical clot disruption, within 6 hours of stroke onset was studied in a randomized, controlled trial of patients with moderately severe (median NIHSS 17) acute ischemic stroke and angiographically proven proximal (M1 or M2) middle cerebral artery occlusion in the...
Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial.\textsuperscript{12} Patients treated were 60\% (relative increase; 15\% absolute) more likely to have a favorable outcome (modified Rankin Scale score, 0–2) and 3 times more likely to have early recanalization of the proximal middle cerebral artery (66\% versus 18\%). As with the intravenous tPA studies, the rate of symptomatic intracranial hemorrhage was increased in the treated group (10\% versus 2\%), but this did not result in higher rates of death or severe disability. Catheter-based therapy has developed further with the use of intra-arterial tPA and microwire clot disruption and with the development of snares and aspiration devices for mechanical withdrawal of the occlusive thrombus.\textsuperscript{13–15} Although the studies of clot retrieval devices have not been controlled, an important finding has been the correlation of good outcomes with early recanalization. Because many patients with proximal arterial occlusions will not have early recanalization after intravenous tPA, the benefit of intravenous tPA followed immediately by intra-arterial therapy is being tested. This approach has been shown to work in selected patients in a case-control study and is being investigated in a randomized controlled trial.\textsuperscript{16–18} With the current state of knowledge, recommendations are in flux. However, specialized centers are applying endovascular techniques within 6 to 8 hours in selected patients with acute stroke, particularly those with contraindications to intravenous therapy and those with proximal vessel occlusion who do not have an immediate response to intravenous therapy.\textsuperscript{5,19}

**Conclusions**

Stroke therapy has been revolutionized over the last 15 years with the successful application of intravenous and intra-arterial thrombolytic therapies. These therapies are now being widely applied successfully, and they hold great promise for future advances. The demand for rapid assessment and decision making and the risk of intracranial hemorrhage continue to pose challenges to practitioners and researchers trying to optimize acute management of stroke. Therefore, it is critical for physicians, facilities, and regional healthcare systems to develop protocols to deliver these therapies optimally. In addition, a fine balance between benefits and risks is inherent in thrombolytic therapy. Therefore, it is critical for physicians and funding agencies to promote and support further research to refine and extend its use.

**Case 1.** This patient presented in the early stages of an acute stroke, apparently caused by cardioembolic occlusion of the left middle cerebral artery. He had no contraindications to thrombolytic therapy (Table 2). He was treated with intravenous tPA 0.9 mg/kg and was monitored closely to control blood pressure and to observe for complications (Table 1). Follow-up magnetic resonance imaging showed a small left middle cerebral artery infarct with sparing of the great majority of the middle cerebral artery territory at risk. He was discharged to a rehabilitation hospital with only mild aphasia and mild right hemiparesis.

**Case 2.** This patient showed no immediate benefit from intravenous tPA with a demonstrated persistent proximal arterial occlusion. Although the optimal role of catheter-based therapies remains undefined, there is strong evidence that early recanalization by these means correlates with improved outcomes, and we elected to take this patient for acute intra-arterial thrombolysis. Excellent recanalization was achieved with mechanical clot retrieval (Figure 1D). Follow-up magnetic resonance imaging showed an
acute infarct in a portion of the territory of the inferior division of the right middle cerebral artery, primarily in areas seen to be infarcted on the pretreatment head CT, but full sparing of the superior division territory. She had an excellent early functional recovery, and she was discharged to a rehabilitation hospital able to ambulate with assistance, with very mild left face, arm, and leg weakness and mild left-sided sensory loss without neglect (National Institutes of Health Stroke Scale score, 3).

Disclosures

None.

References


Thrombolytic Therapy of Acute Stroke
Steven K. Feske

Circulation. 2012;125:2662-2666
doi: 10.1161/CIRCULATIONAHA.111.060087

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/125/21/2662

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/