

Acute stroke therapy: Beyond IV tPA

ANTHONY J. FURLAN, MD*

Medical Director, Cerebrovascular Center, Section of Stroke and Neurocritical Care, Department of Neurology, The Cleveland Clinic Foundation

ABSTRACT

Although intravenous tissue plasminogen activator (IV tPA) has been approved for treating acute ischemic stroke, it must be given within 3 hours of stroke onset and only after ruling out hemorrhagic stroke by computed tomography. Several medical centers are turning to angiography to guide intra-arterial infusion of thrombolytic agents and mechanical endovascular interventions.

Using IV tPA in clinical practice has proved very difficult

IN OUR QUEST to develop practical and effective therapy for acute ischemic stroke, we are moving beyond intravenous infusion of tissue plasminogen activator (IV tPA; alteplase) and are trying various strategies using intra-arterial infusions and mechanical interventions.

tPA FOR STROKE: EFFECTIVE BUT OFTEN IMPRACTICAL

In a landmark study from the National Institute of Neurological Disorders and Stroke (NINDS),¹ 624 patients were randomized to receive either placebo or IV tPA (0.9 mg/kg, maximum 90 mg, 10% as a bolus and the

remainder within 60 minutes) within 3 hours of stroke onset. At 90 days, there was an 11% to 13% absolute increase in essentially full neurologic recovery among treated patients.

But at a price. The rate of symptomatic intracerebral hemorrhage at 36 hours was significantly higher in the tPA group (6.4% vs 0.6%). Although overall mortality was not increased, tPA-related intracerebral hemorrhage is often fatal. The net benefit of tPA was reduced for older patients (age > 77 years) and for more severely affected patients (ie, with a National Institutes of Health Stroke Scale [NIHSS] score > 22).

The Food and Drug Administration (FDA) approved tPA for treating acute ischemic stroke in June 1996, but only for patients meeting the inclusion criteria of the NINDS study. Most important of these: treatment must begin within 3 hours of the onset of stroke, and before this can happen, patients must undergo a computed tomographic (CT) scan to rule out intracerebral hemorrhage (TABLE 1).

Using IV tPA in clinical practice has proved very difficult. For example, in Cleveland hospitals in 1997–1998, only 1.8% of patients admitted with ischemic stroke received IV tPA.²

THE CONTINUING PROBLEM OF INTRACEREBRAL HEMORRHAGE

The number-one problem with thrombolytic therapy remains brain hemorrhage, and we must solve it. In a typical scenario, a patient achieves partial recanalization, recovers neurologically (the “Lazarus phenomenon”), goes to the intensive care unit, develops an intracerebral hemorrhage, and dies. The mortality rate for symptomatic reperfusion hemorrhage is about 90%.

The risk of hemorrhage is higher in patients with more severe strokes and

*The author has indicated that he has received grant or research support from the Possis corporation, serves as a consultant for the Abbott and Lilly corporations, and is on the speakers' bureau of the Bristol-Myers Squibb corporation. This paper discusses therapies that are not approved by the US Food and Drug Administration for the use under discussion.

Medical Grand Rounds articles are based on edited transcripts from Division of Medicine Grand Rounds presentations at The Cleveland Clinic. They are approved by the author but are not peer-reviewed.

**TABLE 1****NINDS inclusion and exclusion criteria for tPA therapy for acute ischemic stroke****Inclusion criteria** (patient must have all three of the following)

- Ischemic stroke within 180 minutes of onset, with a clearly defined time of onset or when the patient was last known to be intact
- Neurologic deficit measurable on the NIH Stroke Scale, and appropriate for such therapy
- CT scan of the brain showing no evidence of intracerebral hemorrhage or signs of significant early infarct

Exclusion criteria (patient must have none of the following)

- Stroke or serious head trauma within the preceding 3 months
- Major surgery within 14 days
- History of intracerebral hemorrhage
- Systolic blood pressure above 185 mm Hg, diastolic blood pressure above 110 mm Hg, or aggressive treatment required to reduce blood pressure to these limits
- Rapidly improving or minor neurologic symptoms
- Symptoms suggestive of subarachnoid hemorrhage
- Gastrointestinal hemorrhage or urinary tract hemorrhage within the previous 21 days
- Arterial puncture within the previous 7 days at a noncompressible site
- Seizure at the onset of the stroke
- Current use of oral anticoagulants
- Prothrombin time greater than 15 seconds
- Heparin within 48 hours preceding the onset of the stroke with an elevated partial thromboplastin time
- Platelet count < 100,000/mm³
- Glucose concentration < 50 mg/dL or > 400 mg/dL

Cautionary signs (not contraindications, but should alert the physician's concern)

- Severe neurologic deficit, with an NIH Stroke Scale score > 22, especially in an elderly patient
- Early signs of acute stroke on CT scan: evidence of large middle cerebral artery involvement with hypodensity, blurring of the gray-white margins, or sulcal effacement in > 1/3 of the middle cerebral distribution

ADAPTED FROM NINDS AND STROKE rt-PA STROKE STUDY GROUP. TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE. N ENGL J MED 1995; 333:1581–1587.

patients over age 77, as seen by comparing the rates in the Prolyse in Acute Cerebral Thromboembolism (PROACT-II)³ and the NINDS¹ studies, and in subgroup analysis of patients in the NINDS study.

Community practice may also not reflect the results of a clinical trial. In Cleveland, the rate of symptomatic hemorrhage was 16% in 1997–1998, although experienced centers are achieving rates of about 6%, similar to the NINDS trial. Recent data from Cleveland indicate the hemorrhage rate here has also fallen to 6%, which reflects a physician learning curve and the institution of a citywide stroke quality improvement program.

■ OPENING THE STROKE TREATMENT WINDOW

The main challenge with tPA is the 3-hour window. By the time a stroke patient recog-

nizes that something is wrong, is transported to a hospital equipped to give this therapy, and undergoes a history, physical examination, and CT scan, it is often too late to start IV tPA.

Could the 3-hour window be extended? While it remains true that “time is brain,” several strategies have been employed to give us more time to treat acute stroke.

Intravenous tPA at 6 hours

Three major trials of IV tPA therapy have been performed with a 6-hour window.^{4–6} All three returned the same finding: no definitive evidence that IV tPA is useful after 3 hours.

Even 3 hours may be too long for IV tPA. Marler et al⁷ re-analyzed the data from the NINDS study and found that most of the benefit of IV tPA was in patients treated within 90 minutes of stroke onset.

■ PROACT: INTRA-ARTERIAL THERAPY IN LESS THAN 6 HOURS

With the limitations of IV tPA in mind, we decided to try a different approach: intra-arterial therapy.

The **PROACT-I trial**⁸ was a pilot study to determine if intra-arterial thrombolysis for acute stroke is safe and effective in restoring blood flow. Patients (N = 105) underwent diagnostic cerebral arteriography and were randomized (N = 46) if the M1 or M2 segment of the middle cerebral artery was occluded (a critical site for emboli from atrial fibrillation) and a microcatheter could be safely advanced to the site of occlusion. Treatment consisted of placebo or prourokinase 9 mg infused directly into the thrombus over 2 hours, plus heparin in a 2,000-U IV bolus followed by 500 U/hour for 4 hours. No adjunctive antithrombotic agents were then allowed for 24 hours.

At 2 hours, 20% of treated patients had achieved grade 3 flow by the criteria of the Thrombolysis in Acute Myocardial Infarction (TIMI) trial in the blocked artery, compared with 2% in the control group, and 67% vs 18% had achieved either TIMI grade 2 or grade 3. (TIMI flow grades go from 0 [completely blocked] to 3 [completely open].)

The **PROACT-II trial**³ demonstrated that intra-arterial thrombolysis not only opened blocked brain arteries but was also clinically effective in 180 patients at 54 medical centers. Patients had a median baseline NIHSS score of 17, making them the most severely affected acute stroke patients ever studied in a thrombolysis clinical trial, and were treated a median of 5.3 hours after stroke onset.

In the treated group, 40% of patients achieved a Rankin score of 2 or less, indicating recovery with no or minimal disability, vs 25% in the control group, a 15% absolute difference and 60% relative difference ($P = .04$).

But again at a price: intracerebral hemorrhage with neurologic deterioration at 24 hours occurred in 10% of treated patients vs 2% of the control patients ($P = .06$). Despite the increased risk of hemorrhage, there was no difference in the 90-day mortality rate: 24% in the treated group and 27% in the control group.

In view of the small size of this study, the FDA has not approved intra-arterial therapy. However, several professional societies have endorsed intra-arterial thrombolysis up to 6 hours from stroke onset as a reasonable alternative therapy in selected acute stroke patients, and many medical centers are using it routinely.⁹ The FDA has asked for a confirmatory study, but many centers are reluctant and already consider it unethical to deny the patients in the control group a proven therapy. Hopefully, PROACT-III will start soon and be able to generate the needed numbers (N = 500) to settle the issue once and for all.

Combined intravenous and intra-arterial thrombolysis

Intra-arterial therapy poses even more logistical problems than intravenous therapy. We and other centers are working out protocols in which patients receive a loading dose of IV tPA and then are sent to the catheterization laboratory if they still have an occlusion within 3 to 6 hours.⁹ The Interventional Management of Stroke study is using a reduced dose of IV tPA (0.6 mg/kg, 15% as a bolus, the rest as a 30-minute infusion up to 60 mg maximum), followed by angiography. If a thrombus is present, the patient receives additional tPA intra-arterially. Combined IV and intra-arterial thrombolysis would allow therapy to be initiated at the community hospital, where patients often present, and then enable patients to be transported to a regional stroke center for intra-arterial therapy if needed.

■ NEWER CLOT-BUSTERS

Besides looking at different ways of giving thrombolytic agents, researchers are also looking at a variety of new agents. Several of these agents are more fibrin-specific and have a longer half-life than tPA so they may be given as a single bolus. It is not clear, however, if this improves the recanalization efficacy and safety of these agents.

Desmoteplase, a thrombolytic agent derived from the vampire bat, is highly selective for fibrin-bound plasminogen. The Desmoteplase in Acute Ischaemic Stroke study is recruiting patients for IV treatment within 9 hours of stroke onset, based on mag-

Intra-arterial prourokinase is not approved, but many centers are using it



netic resonance imaging criteria.

Tenecteplase is undergoing pilot studies in stroke at the University of Virginia.

Glycoprotein (GP) IIb/IIIa inhibitors, which block the final common pathway of platelet aggregation, have demonstrated efficacy in preventing thrombus formation in acute coronary syndromes and percutaneous coronary interventions. In acute ischemic stroke, a dose-escalation study demonstrated that the GP IIb/IIIa inhibitor abciximab is safe when given as a 0.25 mg/kg bolus and 0.125 mg/kg/minute infusion. A phase 2 trial is underway in acute ischemic stroke of less than 6 hours' duration. Some centers are using IIb/IIIa inhibitors as adjunctive therapy with intra-arterial thrombolysis in acute stroke patients.

■ INTERVENTIONAL DEVICES

Just as cardiologists use a number of mechanical interventions to open blocked coronary arteries, stroke researchers are experimenting with new devices and interventions.

The AngioJet catheter system (Possis Medical, Minneapolis, Minn) uses a high-velocity stream of saline directed back into the catheter to create a localized, low-pressure zone at the distal tip. Via the Bernoulli effect, thrombus is trapped, broken up into small particles, and evacuated, literally within minutes. The system is currently approved for use in saphenous vein graft thrombectomy but has been modified for neurovascular use. A problem has been distal embolism of particles.

Another interventional catheter uses ultrasound to loosen the thrombus (Ekos Corp., Bothell, WA), after which a thrombolytic drug can be infused. Laser catheters are also being tested in humans (EndoVasix, Belmont, Calif).

Angioplasty and stenting was performed in a series of 8 patients with symptomatic intracranial vertebrobasilar atherosclerosis reported by Rasmussen et al at The Cleveland Clinic.¹⁰ The patients received aspirin, clopidogrel, heparin, and abciximab. The procedure was technically successful in 7 patients; 1 patient died of a subarachnoid hemorrhage the evening of the procedure. All the patients

who survived were without symptoms up to 8 months later.

■ NEUROPROTECTION THROUGH HYPOTHERMIA

Another strategy to buy more time is neuroprotection. Unfortunately, while many neuroprotectants have worked in animals, all have failed in humans.

Perhaps the most promising neuroprotectant currently under study is hypothermia. Hypothermia has been used since the 1950s to protect tissue during cardiovascular and neurovascular procedures. In several stroke models, cooling to 32 to 34°C for 24 to 48 hours decreased infarct volume and extended the time required for damage to occur, thus limiting ischemic damage and improving outcome.

Hypothermia may exert its effect by reducing glutamate release, free-radical mechanisms, ischemic depolarization, and kinase reactions; by preserving the blood-brain barrier and cytoskeleton; and by suppressing inflammatory mechanisms. Hypothermia may be effective because of this so-called "dirty" neuroprotection as compared with drugs that block only one aspect of the ischemic cascade.

Surface cooling in two small case series of acute stroke patients reduced intracranial pressure and mortality and was associated with improved neurologic outcome compared with concurrent controls. Complications included cardiac arrhythmias, pneumonia, and sepsis. In patients with large hemispheric infarcts, the cerebral edema may be delayed, only to recur during rewarming.

As with interventional stroke devices, the old and clumsy method of surface cooling is being replaced by new endovascular devices. Currently ongoing is the COOL AID trial (Cooling for Acute Ischemic Brain Damage), a phase 2 trial in patients with acute ischemic stroke of less than 12 hours' duration. After thrombolysis, a heat-exchange catheter is introduced into the inferior vena cava, without need for the paralysis or sedation that may account for much of the medical comorbidities seen with other methods of hypothermia. The body is cooled to 32°C.

Endovascular devices for hypothermia are replacing old and clumsy methods of surface cooling



■ NEW IMAGING TECHNIQUES IN ACUTE STROKE

Conventional CT scanning provides very limited information in acute stroke, mainly ruling out hemorrhage. CT perfusion and CT angiography may soon replace conventional CT scans in acute stroke to provide a CT “stroke-o-gram.” A similar approach uses diffusion-weighted and perfusion-weighted MRI to identify brain tissue at risk but still salvageable (“penumbra”). Such a stroke-o-gram provides a much more physiological approach to the stroke treatment time window and will revolutionize how we select therapies for acute stroke. 

■ REFERENCES

1. **NINDS and Stroke rt-PA Stroke Study Group.** Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333:1581–1587.
2. **Katzan IL, Furlan AJ, Lloyd LE, et al.** Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA* 2000; 283:1151–1158.
3. **Furlan A, Higashida R, Wechsler L, et al.** Intra-arterial prourokinase for acute ischemic stroke. The PROACT-II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA* 1999; 282:2003–2011.
4. **Hacke W, Kaste M, Fieschi C, et al.** Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995; 274:1017–1025.
5. **Hacke W, Kaste M, Fieschi C, et al.** Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet* 1998; 352:1245–1251.
6. **Clark WM, Wissman S, Albers GW, et al.** Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. *JAMA* 1999; 282:2019–2026.
7. **Marler JR, Tilley BC, Lu M, et al.** Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology* 2000; 55:1649–1655.
8. **Del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M.** PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. *Stroke* 1998; 29:4–11.
9. **Kidwell CS, Saver JL, Carneado J, et al.** Predictors of hemorrhagic transformation in patients receiving intra-arterial thrombolysis. *Stroke* 2002; 33:717–724.
10. **Rasmussen PA, Perl J 2nd, Barr JD, et al.** Stent-assisted angioplasty of intracranial vertebrobasilar atherosclerosis: an initial experience. *J Neurosurg* 2000; 92:771–778.

■ SUGGESTED READING

Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest* 2001; 119:(suppl 1):300S–320S.

ADDRESS: Anthony J. Furlan, MD, Department of Neurology, S91, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.