Therapy for acute ischemic stroke: the door opens

INTERPRETING THE NINDS RT-PA STROKE STUDY

THE FIRST SUCCESSFUL trial of therapy for acute ischemic stroke, announced December 14, 1995 in the *New England Journal of Medicine*, will forever change the prevalent nihilistic attitude toward treating the third-ranking cause of death and leading cause of neurologic disability in America.

The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group[1] reported that patients given recombinant tissue plasminogen activator (rt-PA) intravenously within 3 hours of the onset of ischemic stroke were at least 30% more likely to have minimal or no disability 3 months subsequently, compared with patients who received placebo. The odds ratio of a favorable outcome with treatment was 1.7 (95% confidence interval [CI] 1.2 to 2.6; $P = .008$). This benefit came at the price of a significantly increased incidence of symptomatic brain hemorrhage within the first 36 hours: 6.4% in the rt-PA group vs 0.6% in the placebo group ($P < .001$). However, the overall mortality was not different between the two groups.

With so much at stake, it is not surprising that this trial has sparked intense debate among those who treat stroke patients. Two issues have created the greatest concern. One worry is that current practices will continue and that rt-PA will not be used, depriving stroke victims of a potentially beneficial therapy. The other is that rt-PA will be given to patients who should not receive it, causing a surge in complications that will overshadow the benefits of rt-PA therapy, thereby negating the positive momentum towards creating a system for treating victims of acute stroke.

WHY SUCCESS AFTER SO MANY FAILURES?

Many previous trials of thrombolysis for acute stroke were unsuccessful and generated an attitude of nihilism that has been difficult to reverse. Why then, after so many failed trials, was the NINDS trial successful? A big part of the answer lies in the definition of "acute." Most trials in the 1970s and 1980s defined "acute" as less than 24 or even 48 hours. We now realize that the therapeutic window closes by 8 hours in most patients. The NINDS trial specified that treatment be started within 180 minutes of the onset of symptoms, the most ambitious therapeutic window in any trial yet. A tremendous effort was required to educate and mobilize patients, families, and medical emergency personnel, a fact that cannot be overemphasized. Indeed, the major reason for ineligibility in acute stroke trials continues to be late presentation to the hospital, and very few hospitals are organized to offer emergency treatment within hours of stroke onset.

WHICH PATIENTS BENEFIT?

The NINDS inclusion criteria were broad, but there were 15 exclusion criteria, most intended to avoid hemorrhagic complications (*Table*). Compared with coronary artery occlusion syndromes (or heart attacks), in which the pathophysiologic features are relatively homogeneous, strokes (or "brain attacks") are quite heterogeneous. This poses a problem, as the short time window for treatment creates pressure that limits the extent of diagnostic testing. To save time, the NINDS investigators per-

TABLE
INCLUSION AND EXCLUSION CRITERIA IN THE NINDS TRIAL*

Inclusion criteria
Ischemic stroke within 180 minutes of onset, with clearly defined time of onset
Neurologic deficit measurable on the NIH stroke scale
Computed tomographic scan of the brain showing no evidence of intracranial hemorrhage
Exclusion criteria
Stroke or serious head trauma within the preceding 3 months
Major surgery within 14 days
History of intracranial hemorrhage
Systolic blood pressure > 185 mm Hg or diastolic blood pressure > 110 mm Hg
Aggressive treatment required to reduce blood pressure to the specified 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 at a noncompressible site within the previous 7 days
Seizure at the onset of the stroke
Use of oral anticoagulants
Prothrombin time > 15 seconds
Heparin within the 48 hours preceding the onset of the stroke with an elevated partial thromboplastin time
Platelet count < 100 000/mL^3
Glucose concentration < 50 mg/dL (2.7 mmol/L) or > 400 mg/dL (22.2 mmol/L)

*NINDS, National Institute of Neurological Disorders and Stroke, reference 1

formed only a history, examination, and CT scan before treatment.

The benefit in outcome with rt-PA in the NINDS trial seemed to apply to all stroke subgroups (small-vessel occlusive, cardioembolic, large-vessel occlusive, and other), but this warrants further analysis. Other thrombolytic trials that included angiographic studies have demonstrated that the efficacy of clot lysis is related to the site of occlusion as well as the volume, age, and composition of the clot. Recanalization rates are much lower with occlusions in large vessels than in smaller ones, and with intravenous than with intra-arterial regimens. With either type of regimen started within 8 hours, the recanalization rate for internal carotid artery occlusions is less than 20%. With intra-arterial regimens, the reperfusion rate in proximal middle cerebral occlusions exceeds 60%. The initial recanalization rate with intra-arterial thrombolysis for basilar occlusion approaches 80% but is often complicated by rethrombosis at the site of residual stenosis, and the overall mortality rate exceeds 75%. Lacunar infarcts result from occlusion of arteries of 100 to 200 μm, which is smaller than the resolution of angiography. Unfortunately, although angiography provides important information on the specific mechanism of many strokes, it requires precious time and may not be realistic to perform in trials with very short treatment windows.

Fewer than 5% of all patients with acute ischemic stroke would meet the entry requirements for the NINDS study. In fact, in the trial, about 25 patients were screened for every one entered. Again, time was the major limiting factor. The delay in bringing stroke victims to treatment could significantly decrease with coordinated public educational efforts in the recognition of stroke signs and symptoms and modifications in emergency-care systems, including clinical pathways guidelines, early-notification "stroke beepers," and efficient use of CT scanning. Indeed, clinical trials have been the strongest stimulus for such necessary changes at many medical centers.

WHICH PATIENTS ARE AT EXCESS RISK?

Controversy surrounds the precise definition of the therapeutic window and will continue until new technologies are developed that can accurately differentiate irreversibly infarcted tissue from the penumbra of "idling" neurons that could respond to reperfusion. The importance of defining a salvageability window is magnified by the fact that the time elapsed to treatment powerfully predicts the risk of thrombolytic therapy.

One of the first trials of intravenous recombinant tissue plasminogen activator demonstrated that the

incidence of symptomatic intracranial hemorrhage was significantly higher for patients treated between 6 and 8 hours after symptoms began than in those treated within 6 hours.[2] Three recent trials of intravenous streptokinase were halted because of excessive mortality from intracranial hemorrhage. The Multicenter Acute Stroke Trial-Italy[3] and the Australian Streptokinase trial[4] both suggested that most excess hemorrhages and early deaths occurred in patients treated after 3 hours, while in those treated in less than 3 hours there was a nonsignificant trend toward better outcome.

The European Cooperative Acute Stroke Study group (ECASS) evaluated rt-PA given intravenously within 6 hours of onset of symptoms and reported no benefit in an intent-to-treat analysis.[5] There was, however, a significant improvement in clinical outcome at 3 months in a "target population" that was derived by excluding 109 protocol violators (17.4%) from the 620 patients treated. Finding this "target population" depended on the accurate recognition of early CT signs of infarction by a panel of experts. In subsequent analyses, early mortality was also significantly higher in patients older than 70 years and patients with serious neurologic deficits (a Scandinavian Stroke Scale score of 14 or less). A prospective analysis of early CT signs, age, and severity of deficit is needed to refine selection criteria.

WHAT DO WE DO NOW?

We must start thinking of "brain attacks" in the same way we presently view heart attacks and mobilize our resources appropriately. Patients presenting within 180 minutes who meet the NINDS criteria (*Table*) should receive rt-PA therapy. Because the time to treatment is critical, one must carefully determine and document the time that symptoms began. Patients who awaken with a deficit should be timed from the last moment they were witnessed to be intact. A knowledgeable person should inspect the CT scan for early signs of major infarction such as hypodensity or obscuration of the gray-white junction as well as any intracranial hemorrhage. Strict management of blood pressure is required, and given that the highest risk for intracranial bleeding is within the first 36 hours of therapy, patients should be monitored in an intensive care unit.

FUTURE DIRECTIONS

Alternative thrombolytic agents and delivery techniques are presently under study. Multimodal therapies designed to attack multiple sites of the ischemic cascade are needed; the first of these might be the combination of cytoprotective agents and thrombolytic agents. Novel neuroimaging technologies are needed to rapidly determine the site of occlusion and to distinguish ischemic from infarcted tissue. Although in many ways we are following the path blazed by interventional cardiologists, we are far from an era of megatrials of acute stroke. As Louis Caplan cautioned at the recent 21st International Joint Conference on Stroke and Cerebral Circulation in San Antonio, "it is easy to let overenthusiasm blur our judgement...the door has opened...but we must peer in."

CATHY A. SILA, MD
Associate Medical Director
Cerebrovascular Center
ANTHONY J. FURLAN, MD
Medical Director
Cerebrovascular Center
The Cleveland Clinic Foundation

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