Intravenous Thrombolytic Therapy for Acute Ischemic Stroke

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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author’s clinical recommendations.

Intravenous Thrombolytic Therapy for Acute Ischemic Stroke

An 81-year-old man arrived at the emergency department at 9:15 a.m. with speech difficulty and weakness on the right side. He had awakened that morning without symptoms. During breakfast at 8 a.m. his wife saw him slump over and fall from the chair to the floor. He was unable to speak and could not move his right arm or leg. She called 911, and he was transported to the emergency department. He made a few attempts to speak, but his speech was unintelligible. He could move his right arm and leg but could not lift either limb off the bed. Computed tomography (CT) of the brain showed no hemorrhage and no early ischemic changes. Blood pressure was 160/90 mm Hg. His platelet count, glucose level, and prothrombin time were all normal. After the patient returned from imaging at 10 a.m., a neurologist was consulted, who confirmed the presumptive diagnosis of acute ischemic stroke and recommended immediate initiation of intravenous thrombolytic therapy.

The Clinical Problem

Stroke is the leading cause of disability among adults in the United States. Despite advances in preventive strategies and initial therapy for stroke, nearly 800,000 strokes occur per year in the United States, and 87% of all strokes worldwide are ischemic in origin (caused by in situ thrombosis, embolism, or systemic hypoperfusion). The risk of stroke is higher among men than among women, among blacks than among whites, and in older than in younger age groups.

In 2007, stroke accounted for 1 of every 18 deaths in the United States. According to one report, the 30-day mortality for ischemic stroke was 8 to 12% for people 45 to 64 years of age. In the Framingham Heart Study, among survivors of an ischemic stroke who were 65 years of age or older and were evaluated 6 months after the event, 50% had some evidence of hemiparesis, 30% were unable to walk without assistance, 19% had aphasia, and 26% were institutionalized. The estimated direct medical cost of stroke in the United States was $25 billion in 2007.

Pathophysiology and Effect of Therapy

Ischemic stroke results from vascular occlusion that reduces cerebral blood flow to the area of brain perfused by the occluded artery. In either thrombotic or embolic stroke, such occlusion is caused by obstruction of the artery by thrombus. If the reduction in blood flow is sufficiently severe, a series of events occurs at the cellular level that leads to infarction. The release of excitatory amino acid neurotransmitters, the influx of calcium, the generation of oxygen free radicals, membrane depolarization, and eventually, the loss of membrane integrity are all
thought to contribute to the detrimental effects of ischemia. A newer concept of ischemic injury considers neurons, astrocytes, and vascular structures and their interactions to be a neurovascular unit. Disturbance of the complex signaling and interactions between components of the neurovascular unit probably plays an important role in ischemic brain injury. Matrix metalloproteinase 9 is up-regulated during ischemia and may contribute to the breakdown of the blood–brain barrier and hemorrhagic transformation. Similarly, oxidative stress and inflammation are triggered by ischemia and contribute to the process of cellular injury and infarction.

In experimental models of stroke, both the duration and the severity of ischemia determine the threshold for irreversible damage. Magnetic resonance imaging (MRI) and CT perfusion studies in patients with acute stroke suggest that the ischemic areas of the brain may in some cases remain viable for as long as 24 hours, with the potential for the restoration of normal function after reperfusion (Fig. 1). However, the benefit of extending the treatment window for patients selected on the basis of the results of perfusion imaging has not been validated by clinical studies.

Tissue plasminogen activator (t-PA) is a serine protease that acts by enhancing the conversion of inactive plasminogen to active plasmin. Plasmin acts on fibrin clots, causing dissolution and lysis. The activity of t-PA is greatly enhanced in the presence of fibrin, increasing fibrinolysis specifically at the site of thrombosis. In vivo, t-PA is released by endothelial cells; in contrast, exogenously administered t-PA is derived from the application of recombinant DNA technology and is thus designated recombinant t-PA (rt-PA). Unlike first-generation plasminogen activators such as streptokinase and urokinase, rt-PA is fibrin-selective and preferentially activates fibrin-bound plasminogen. Although rt-PA is inhibited by plasminogen activator inhibitor type 1 (PAI-1) in plasma, the capacity of PAI-1 to bind rt-PA is rapidly exceeded when the drug is administered systemically, thus increasing the risk of bleeding. The half-life of rt-PA in the circulation is about 4 minutes, but the physiological effect may last longer as a consequence of fibrin binding.

Clinical Evidence

In 1996, the Food and Drug Administration (FDA) approved the use of intravenous rt-PA for the treatment of acute ischemic stroke after the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator (NINDS rt-PA) Stroke Study was completed. In part 1 of this study, 291 patients with acute ischemic stroke were randomly assigned, within 3 hours after the onset of the stroke, to either intravenous rt-PA or placebo. The primary end point was the rate at 24 hours of either complete neurologic recovery or neurologic improvement, as indicated by an improvement of at least 4 points above baseline values on the National Institutes of Health Stroke Scale (NIHSS) (a 42-point scale that quantifies neurologic deficits in 11 categories, with higher scores indicating more severe deficits). In this part of the trial, no significant difference was seen in the primary end point between patients receiving rt-PA and those receiving placebo (51% and 46%, respectively; relative risk with rt-PA, 1.1; 95% confidence interval [CI], 0.8 to 1.6; P=0.56).

In part 2 of this study, an additional 333 patients were enrolled and randomly assigned to the same two groups. The primary end point was the rate of complete or nearly complete recovery at 90 days, as indicated by a combined assessment of four separate neurologic-outcome scales. In this part of the trial, the rate of a favorable outcome was significantly greater with intravenous rt-PA than with placebo (odds ratio, 1.7; 95% CI, 1.2 to 2.6; P=0.008). This benefit was sustained at 6 months and at 1 year.

Three additional randomized trials showed no benefit of intravenous rt-PA as compared with placebo. These trials included the European Cooperative Acute Stroke Study (ECASS), ECASS II, and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial. These trials differed from the NINDS study in several important respects. Most notably, patients could be enrolled up to 6 hours after the onset of stroke, and only 14% of patients were treated within 3 hours after the event. In contrast, in the NINDS trial, almost all patients were treated within 3 hours and 48% within 90 minutes after stroke onset.

In the subsequent ECASS III, 821 patients who presented between 3 and 4.5 hours after the onset of stroke were randomly assigned to intravenous rt-PA or placebo. The primary outcome was disability at 90 days, dichotomized as either a favorable outcome (a score of 0 or 1) or an unfavorable outcome (a score of 2 to 6) according to the
modified Rankin scale (which ranges from 0 to 6, with 0 indicating no symptoms and 6 indicating death). In ECASS III, patients were excluded if they were older than 80 years of age, had had a severe stroke (defined as an NIHSS score >25 or hypodensity of more than one third of the middle-cerebral-artery territory on CT scanning), had received prior treatment with anticoagulants, regardless of the international normalized ratio (INR), or had a history of both stroke and diabetes. At 90 days, significantly more patients treated with rt-PA had favorable outcomes, as com-

Figure 1. CT Perfusion Imaging in a Patient with Stroke, before and after Thrombolysis with Recombinant Tissue Plasminogen Activator (rt-PA).

Standard CT images without contrast material (left two images) and CT perfusion images obtained during the first pass of an intravenous bolus of iodinated contrast material (right six images) are shown. Images were obtained before (Panel A) and after (Panel B) thrombolysis with rt-PA. Mathematical algorithms are used to create, from the perfusion data, maps of the mean transit time (MTT) (the difference in time between arterial inflow and venous outflow), cerebral blood volume (CBV), and cerebral blood flow (CBF). The CT scan without contrast material that was obtained before thrombolysis shows hypodensity in the area of the left caudate nucleus (arrow), with loss of definition between gray matter and white matter. The scan obtained after thrombolysis shows a central area of hypodensity in the area of the left caudate nucleus, which is consistent with hemorrhage within the infarct zone, surrounded by an area of hypodensity (arrow), which is consistent with infarction. The CT perfusion maps in Panel A, obtained before thrombolysis, show prolonged MTT (arrow), decreased CBV (arrow), and decreased CBF (arrow) in the left hemisphere. There is some degree of mismatch between the CBV map (which emphasizes irreversible injury, primarily in the area of the left caudate nucleus) and the CBF map (which shows an extensive area of abnormality throughout the left hemisphere, indicating tissue at risk). The CT perfusion maps in Panel B, obtained after thrombolysis, show some improvement in MTT, CBV, and CBF in most areas, although the focus of hypoperfusion in the area of the left caudate nucleus persists (arrows), which is consistent with the area of infarction shown on the CT scan obtained without contrast material. In these images, the color spectrum indicates the spectrum of values for each quantity. On the MTT map, the areas of fastest transit time appear red and those of slowest transit time appear blue. On the CBV and CBF maps, the area of greatest blood volume or blood flow appear red and those of least blood volume or blood flow appear blue. Although quantitative values can be assigned to these data, CT perfusion images are usually interpreted qualitatively by comparing areas of normal with areas of abnormal perfusion. Areas without detectable perfusion are black. A denotes anterior, and R right.
pared with those given placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% CI, 1.02 to 1.76; P=0.04).

**Clinical Use**

Intravenous administration of t-PA within 3 hours after the onset of stroke increases the probability of a favorable outcome. Recommended protocols for selecting patients for treatment with intravenous rt-PA are adapted from the inclusion and exclusion criteria from the NINDS rt-PA trial (Table 1). On the basis of results of ECASS III, some stroke centers now treat patients who present from 3 to 4.5 hours after stroke onset; however, at present, the FDA has approved only rt-PA treatment delivered within 3 hours after stroke onset.

The timing of the onset of stroke should be determined with as much certainty as possible by obtaining first-hand information. If the onset was not observed, the time when the patient was last seen to be neurologically normal should be considered the time of stroke onset. Although this recommendation may exclude some eligible patients, it ensures that those whose stroke occurred outside the time limit for a favorable risk-to-benefit ratio will not be treated.

A rapid examination with the use of the NIHSS will help to quantify the neurologic deficit. Many protocols exclude patients who have mild deficits, since their prognosis for recovery is good without thrombolytic therapy. However, treatment should be initiated on the basis of the assessment of a disabling deficit rather than on a defined lower limit for the NIHSS score. For example, isolated aphasia or hemianopia is a disabling deficit despite an NIHSS score of 2 or 3.

Rapidly resolving deficits may complicate decision making. If the residual deficit continues to be disabling, treatment should be undertaken despite the improvement. Occasionally, rapid recovery is later followed by clinical worsening. Patients should therefore be observed closely and reevaluated frequently during the first 24 hours after the onset of stroke.

Another common concern regarding eligibility for intravenous thrombolysis is poorly controlled blood pressure. In patients receiving intravenous rt-PA, markedly elevated blood pressure may increase the risk of hemorrhage. Current guidelines recommend treatment to achieve a systolic blood pressure of 185 mm Hg or lower and a diastolic blood pressure of 110 mm Hg or lower before intravenous rt-PA is administered.

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**Table 1. Inclusion and Exclusion Criteria for Intravenous t-PA Therapy in Patients with Acute Ischemic Stroke.*

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>Diagnosis of ischemic stroke causing measurable neurologic deficit</td>
<td>Head trauma or prior stroke within the previous 3 mo</td>
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<tr>
<td>Onset of symptoms &lt;3 hr before start of treatment (or, in selected cases, &lt;4.5 hr†)</td>
<td>Symptoms suggestive of subarachnoid hemorrhage</td>
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<tr>
<td>Age ≥18 yr</td>
<td>Arterial puncture at noncompressible site within the previous 7 days</td>
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<tr>
<td>Relative exclusion criteria, depending on risk:benefit ratio‡</td>
<td>History of intracranial hemorrhage</td>
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<tr>
<td>Only minor or rapidly improving stroke symptoms (clearing spontaneously)</td>
<td>Elevated blood pressure (systolic, ≥185 mm Hg, or diastolic, ≥110 mm Hg) that has not responded to antihypertensive treatment</td>
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<tr>
<td>Seizure at onset with postictal residual neurologic impairments</td>
<td>Evidence of active bleeding on examination</td>
</tr>
<tr>
<td>Major surgery or serious trauma within the previous 14 days</td>
<td>Acute bleeding diathesis, including but not limited to the following:</td>
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<tr>
<td>Gastrointestinal or urinary tract hemorrhage within the previous 21 days</td>
<td>Platelet count ≤100,000/mm³</td>
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<tr>
<td>Acute myocardial infarction within the previous 3 mo</td>
<td>Heparin received within 48 hours, resulting in aPTT ≥upper limit of normal</td>
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* Adapted from Jauch et al. The abbreviation aPTT denotes activated partial-thromboplastin time, INR international normalized ratio, PT prothrombin time, and rt-PA recombinant tissue plasminogen activator.
† This criterion is based on the results of European Cooperative Acute Stroke Study III, in which the onset of symptoms was between 3 and 4.5 hours and which excluded patients older than 80 years of age, those with severe stroke (defined by a score ≥25 on the National Institutes of Health Stroke Scale), those receiving anticoagulant therapy regardless of the INR, and those with both diabetes and prior stroke.
‡ Recent experience suggests that under some circumstances, with careful consideration and weighing of the risks versus benefits of rt-PA administration, patients may receive fibrinolytic therapy despite one or more of the listed relative contraindications.
A CT scan of the brain should be obtained before the start of treatment and examined for hemorrhage or early ischemic changes. If a focal area of low density is seen that involves more than one third of the middle-cerebral-artery territory, most treatment protocols recommend withholding thrombolytic therapy, because in some studies this finding (which suggests irreversible injury) has been predictive of subsequent hemorrhagic transformation of the infarct.\textsuperscript{24,29} Laboratory studies that should be obtained before the initiation of thrombolytic therapy include, at a minimum, a platelet count, measurement of glucose levels, and assessment of the prothrombin time. The platelet count should be greater than 100,000 per cubic millimeter, the prothrombin time less than 15 seconds (or the INR <1.7), and the glucose level greater than 50 mg per deciliter (2.7 mmol per liter) before rt-PA is administered.

The patient and family members must be informed of the benefits and risks of intravenous rt-PA therapy before it is initiated. Specifically, they should be told that the benefits include an absolute increase in the odds of a good outcome of 11 to 13 percentage points and a 6% risk of intracranial hemorrhage possibly causing neurologic worsening or death. Some hospitals choose to use a formal consent form, but at a minimum, the consent process should be documented in the medical record.\textsuperscript{28}

The FDA-approved dose of intravenous rt-PA is 0.9 mg per kilogram of body weight, with a maximum dose of 90 mg. A bolus of 10% of the dose is given over a period of 1 minute, with the remainder infused over a period of 60 minutes. Weight should be determined as reliably as is possible. Reports of treatment with a lower dose of rt-PA (0.6 mg per kilogram) in Japan suggest that it has similar efficacy but the lower dose has not yet been assessed in large, randomized trials.\textsuperscript{30,31}

Third-generation plasminogen activators, such as tenecteplase and desmoteplase, are more fibrin-specific than rt-PA and cause less activation of systemic lytic activity.\textsuperscript{32} These agents have been tested in early-phase trials, with mixed results.\textsuperscript{33-37} However, their clinical efficacy has not been established, and neither agent should be used in patients with acute ischemic stroke.

For the first 24 hours after treatment, patients receiving rt-PA should be closely monitored in a specialized stroke unit. If a stroke unit is not available, admission to an intensive care unit is warranted so that the patient can be evaluated frequently by the nursing staff. Blood pressure should be checked every 15 minutes for the first 2 hours, every 30 minutes for the next 6 hours, and then every hour for 16 hours. Antihypertensive therapy with labetalol or, if necessary, intravenous nicardipine should be administered to maintain blood pressure at a level below 180 mm Hg systolic and 105 mm Hg diastolic.\textsuperscript{18,28} Neurologic examination with the use of the NIHSS should be performed every 15 minutes for the first 2 hours, every 30 minutes for the next 6 hours, and then every hour for 16 hours. If a change in neurologic status is noted, the rt-PA infusion should be discontinued and a CT scan obtained. No anticoagulant or antiplatelet therapy should be given for the first 24 hours after treatment with intravenous rt-PA. If a CT scan at 24 hours shows no evidence of hemorrhage, antithrombotic therapy directed at secondary stroke prevention and tailored to the presumed cause of the stroke should be started.

In some stroke centers, a CT angiogram is obtained after intravenous rt-PA has been administered in order to examine the intracranial vasculature for persistent arterial occlusions. In patients with persistent arterial occlusion, one option is an intraarterial intervention: lytic therapy, mechanical clot disruption with the use of various endovascular devices, or both. Although this approach is not approved by the FDA in the treatment of acute stroke, a randomized, controlled trial has suggested a potential benefit from intraarterial lytic therapy.\textsuperscript{38} However, intraarterial interventions should be carried out only at experienced stroke centers.

In one U.S. study,\textsuperscript{39} the cost of rt-PA was estimated to be $2,750. In similar studies, the costs were £480 in the United Kingdom\textsuperscript{40} and $1,647 U.S. in Australia.\textsuperscript{41} Cost-effectiveness analyses in general suggest that rt-PA therapy is more expensive than standard care for ischemic stroke in the short term, owing to the cost of the drug and the need for additional resources, but it is associated with lower costs in the long term, since it reduces the risk of subsequent disability.

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**ADVERSE EFFECTS**

The major complication of thrombolytic therapy for acute stroke is hemorrhage. Symptomatic intracranial hemorrhage occurs in 1.7 to 8.0% of treated patients.\textsuperscript{11,17,42-44} Patients with severe...
stroke have a greater likelihood of hemorrhage, but there is no evidence that this subgroup does not benefit from intravenous rt-PA. Symptomatic hemorrhage is not increased in the elderly, but outcomes are worse and mortality is increased. In addition to age and NIHSS score, other independent risk factors for symptomatic intracranial hemorrhage include hypodensity on CT scanning, elevated serum glucose levels, and persistence of proximal arterial occlusion for more than 2 hours after administration of the rt-PA bolus. Hemorrhagic transformation of ischemic infarcts without clinical change (asymptomatic hemorrhage) occurs more frequently than symptomatic hemorrhage and may be associated with reperfusion and, in some cases, clinical improvement. Serious systemic (extracranial) hemorrhage has been reported in 0.4 to 1.5% of patients. Recommendations for the treatment of intracranial or serious systemic bleeding after thrombolytic therapy often include the administration of cryoprecipitate and platelets, although evidence-based guidelines for such an approach are lacking.

Angioedema of the tongue, lips, face, or neck occurs in 1 to 5% of patients receiving intravenous rt-PA. In most cases, the symptoms are mild and resolve rapidly. Concomitant use of angiotensin-converting–enzyme inhibitors is strongly associated with this complication. Treatment includes glucocorticoids and antihistamines. In rare cases, edema of the pharynx is sufficiently severe to compromise breathing, and intubation may be necessary.

**Areas of Uncertainty**

More than half the patients with ischemic stroke who are treated with intravenous rt-PA do not have complete or near-complete recovery (defined as a score of 0 or 1 on the modified Rankin scale). Lack of recovery may reflect an absence of reperfusion of the occluded artery or reperfusion that occurs too late to restore function. Advanced imaging techniques that involve multimodal MRI or CT (Fig. 1) have the potential to distinguish reversible ischemic injury from irreversible infarction and thus to identify patients who are likely to benefit from thrombolytic therapy. By identifying extensive areas of established infarction, such imaging methods may also help in selecting patients who are at high risk for intracranial hemorrhage and should therefore not be treated with intravenous rt-PA. However, whether the additional time needed for advanced imaging prior to thrombolysis is offset by improved outcomes must be established in appropriately designed clinical trials. At this time, these imaging methods cannot be recommended for routine clinical use. If a reliable pattern of reversibility can be identified, imaging might also be useful when the interval between the onset of stroke and presentation is prolonged or the time of onset is not known.

Transcranial Doppler ultrasonography, which has been used in some observational studies to monitor the effect of lytic therapy, was shown in these studies to be associated with a high rate of recanalization of the occluded stroke-related artery. Transcranial ultrasonography was subsequently evaluated in several small trials and was shown to enhance the lytic effect of rt-PA, although some studies have suggested an increased rate of hemorrhage with transcranial ultrasonography. This approach, called sonothrombolysis, has been implemented clinically as an adjunct to rt-PA administration at some stroke centers.

**Guidelines**

Guidelines for the management of acute stroke issued by the American Heart Association (AHA) and the European Stroke Organization recommend treatment with intravenous rt-PA for patients who meet the stated inclusion criteria, including presentation within 3 hours after the onset of stroke, and who do not meet any of the stated exclusion criteria. Both groups have recently updated their guidelines to extend the treatment window to 4.5 hours. The AHA Science Advisory and Coordinating Committee also recommends that treatment within the 3-hour to 4.5-hour time window be limited to patients who do not meet any of the ECASS III exclusion criteria. An American Academy of Emergency Medicine (AAEM) position statement adopted in 2002 concluded that intravenous rt-PA should not be considered the standard of care, citing the lack of data from trials confirming the NINDS study findings as well as concerns raised about the study. Physicians were advised to use their discretion when deciding whether to use rt-PA. After the results of the ECASS III were published, an updated clinical practice statement from the AAEM stated that intravenous rt-PA is a reasonable option after the results of the ECASS III were published, an updated clinical practice statement from the AAEM stated that intravenous rt-PA is a reasonable option.
treatment option when used in academic centers and primary stroke centers.\textsuperscript{71} A policy statement approved by the board of directors of the American College of Emergency Physicians in 2002 endorsed the use of intravenous rt-PA when it is administered according to the guidelines established by the NINDS study.\textsuperscript{72}

### Recommendations

The patient described in the case vignette meets all the inclusion criteria for treatment with intravenous rt-PA. Assuming that further history taking reveals no pertinent findings, he also has no contraindications to treatment. Evidence from clinical trials does not suggest that persons older than 80 years of age do not benefit from intravenous rt-PA. He completed evaluation in the emergency department 2 hours after the onset of the stroke, and within the FDA-approved 3-hour window, and the probability of recovery is greater the more rapidly treatment can be administered. Once consent has been obtained from his wife, I would elect to proceed with intravenous rt-PA therapy at the standard dose of 0.9 mg per kilogram, with 10% given as a bolus and the remainder infused over a 60-minute period. After the administration of intravenous rt-PA, the patient should be admitted to a specialized stroke unit for monitoring and additional workup to determine the cause of the stroke.

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