Urgent Therapy for Stroke
Part I. Pilot Study of Tissue Plasminogen Activator Administered Within 90 Minutes

Thomas G. Brott, MD; E. Clarke Haley Jr., MD; David E. Levy, MD; William Barsan, MD; Joseph Broderick, MD; George L. Sheppard, MD; Judith Spilker, RN; Gail L. Kongable, CCRN; Sandra Massey, RN; Robert Reed, MD; and John R. Marler, MD

Background and Purpose: Thrombolytic agents hold theoretical promise as therapy for cerebral infarction. This study was designed to evaluate the safety of tissue plasminogen activator, to accomplish urgent patient treatment, and to estimate potential efficacy of tissue plasminogen activator.

Methods: Following neurological evaluation and computed tomography of the brain, patients with acute ischemic stroke were evaluated and treated with intravenous tissue plasminogen activator under an open-label, dose-escalation design within 90 minutes from symptom onset. End points examined included symptomatic and asymptomatic intracranial hematoma, systemic hemorrhage, and neurological outcome at 2 hours, 24 hours, and 3 months.

Results: Seventy-four patients were treated within 90 minutes of symptom onset over seven dose tiers of tissue plasminogen activator, ranging from 0.35 mg/kg to 1.08 mg/kg. Intracranial hematoma with associated neurological deterioration occurred in three patients and was related to increasing doses of tissue plasminogen activator (p=0.045). Intracranial hematoma did not occur in any of the 58 patients treated with ≤0.85 mg/kg. Major neurological improvement occurred in 22 patients (30%) at 2 hours from the initiation of tissue plasminogen activator and in a total of 34 patients (46%) at 24 hours, but major neurological improvement was not related to increasing doses of tissue plasminogen activator or to stroke type.

Conclusions: Patients with acute stroke can be evaluated and treated within 90 minutes. Tissue plasminogen activator for acute ischemic infarction is not without risk, but the potential for clinical benefit justifies a randomized clinical trial. To date, differences in hemorrhagic risk or neurological benefit of tissue plasminogen activator for particular ischemic stroke types are not apparent (Stroke 1992;23:632-640)

KEY WORDS • cerebral ischemia • plasminogen activator, tissue-type • thrombolytic therapy

A ngiographic studies of ischemic cerebral infarction suggest that acute thrombus formation and arterial occlusion are the critical pathological events for 70% or more of stroke patients. Evidence from animal studies suggests that ischemic brain injury will occur when arterial occlusion continues longer than 2-3 hours and that an increasing amount of brain is infarcted if occlusion persists beyond this time. Although the time course for evolution of brain infarction is not precisely known in humans, previous therapeutic trials for ischemic stroke have not sought to treat patients within what may be an early “window of opportunity.”

Thrombolytic agents hold theoretical promise as therapy for acute ischemic stroke, provided that they can be delivered soon after symptom onset. Recombinant tissue plasminogen activator (rt-PA) is a serine protease that cleaves the arginine-valine bond of plasminogen, resulting in the active proteolytic enzyme plasmin; rt-PA is relatively clot-specific in that its activity is enhanced approximately 400-fold when bound to fibrin. In humans, rt-PA infusion can induce lysis of pathological thrombi in the setting of acute myocardial infarction, unstable angina, acute pulmonary embolism, and peripheral arterial occlusion.

We report an open-label study of rt-PA as urgent treatment for acute cerebral infarction. The primary objective of the study was to evaluate the safety of rt-PA, given at successively higher doses, in patients with acute ischemic stroke. The two secondary objectives were 1) to accomplish patient evaluation and treatment within 90 minutes from symptom onset and 2) to estimate potential therapeutic efficacy.
Subjects and Methods

Patients with acute ischemic stroke were recruited at the Cornell University Medical College, the University of Virginia Medical Center, the Winchester Medical Center (Virginia), the University of Cincinnati Medical Center, and eight other Greater Cincinnati hospitals from February 1987 through September 1989. Patients aged 18–80 years with acute cerebral ischemia producing a serious measurable deficit, the onset of which could be confidently established to be within 90 minutes before treatment could begin, were eligible for entry. Patients were excluded because of onset of symptoms on awakening from sleep, sensory loss or ataxia alone, intracranial bleeding detected on a pretreatment head computerized tomographic (CT) scan, clinical presentation suggesting subarachnoid hemorrhage even if the head CT scan was normal, pregnancy, therapeutic anti-coagulation or a prothrombin time (PT) >15 seconds, a platelet count of <100,000/mm³ or known bleeding diathesis (patients receiving “mini-dose” heparin were eligible if the partial thromboplastin time [PTT] immediately before treatment was normal), a history of trauma or significant surgery within the previous 14 days, a history of gastrointestinal or urin ary tract hemorrhage within 21 days, lumbar puncture or arterial puncture of a noncompressible site within the previous 7 days, a pretreatment blood pressure >200 mm Hg systolic or >120 mm Hg diastolic, previous cerebral hemorrhage or ischemic infarction within 3 months, other serious medical illness that might interfere with the study, and inability to obtain informed consent. The exclusion criteria were changed following occurrence of two major hemorrhagic complications. Patients with a mean arterial blood pressure >133 mm Hg were excluded, as were patients with recent transmural myocardial infarction and evidence of pericarditis. All final determinations regarding patient eligibility were made by a neurological investigator on call.

All patients received initial pretreatment medical and neurological examinations, electrocardiogram, unenhanced head CT scan, and screening blood work, including a complete blood count and platelet count, electrolytes, glucose, blood urea nitrogen, PT, and PTT. A standardized neurological examination using the National Institutes of Health (NIH) Stroke Scale was performed immediately before treatment and at 30 minutes, 60 minutes, 2 hours, 24 hours, 48 hours, 7–10 days, and 3 months after initiation of treatment. The NIH Stroke Scale score is zero for a normal patient and 42 for a patient with all items maximally impaired (Figure 1). Head CT scanning was repeated at 18–30 hours, 7–10 days, and 3 months. Any evidence of intracranial bleeding was noted; volumes of intracerebral hematomas and infarct sizes were measured using planimetric techniques. For stroke type classification, standard criteria were used (see “Appendix”), and the assignment of stroke type was made by one of the investigators.

To accomplish treatment within 90 minutes, methods for rapid patient identification, transport, and evaluation were emphasized (Table 1). During the informed consent process, the potential risks of thrombolytic therapy were carefully explained to the patient; the family was involved in all instances in which the patient was mentally impaired and whenever possible in circumstances in which the patient was mentally intact, so that the nature of the study and the potential risks were clearly understood. Each of the institutions involved in the study provided institutional review board approval. After informed consent, rt-PA (alteplase; supplied by Genentech, Inc.) was administered intravenously, initially over 60 minutes. The experience at each dose tier was reviewed by an independent safety and monitoring committee (John Hallenbeck, MD, PhD; Thomas Price, MD; and David Stump, MD) before proceeding to the next dose. Binding criteria for dose advancement or discontinuation of the study were not thought to be feasible given the unavailability of safety information regarding rt-PA and stroke in 1986. Accordingly, decisions regarding numbers of patients per dose tier, advancement in dose, calculation of dose, duration of dose, and use of a bolus were made on a consensus basis among members of the safety and monitoring committee and the investigators. Several nonbinding guidelines were established. The occurrence of two major bleeding complications per group of six consecutive patients was considered justification to decrease the dose by one dose tier pending further review and recommendations of the safety and monitoring committee (e.g., this occurred for the dose of 0.95 mg/kg administered over 60 minutes, and therefore only three patients were treated at that dose); the occurrence of no hematomas per group of six or more consecutive patients supported moving to a higher dose tier, but larger numbers of patients per dose tier were thought advisable for higher doses. The initial 52 patients received a 60-minute infusion, and the remaining patients received a 90-minute infusion; the longer infusion time was hoped to decrease the likelihood of hemorrhagic complications. For the first three dose tiers (Table 2) the patients received rt-PA on a mg/kg basis with a maximum of 25 mg, 40 mg, and 60 mg. Higher doses were calculated on a mg/m² basis to decrease the total dose received by obese patients; these doses have been converted in Table 2 to average mg/kg. The highest dose tier (1.08 mg/kg) was discontinued because of hemorrhagic complications at lower doses occurring in a parallel study of patients treated 91–180 minutes from symptom onset. For all patients, heparin was not permitted for the initial 30 minutes after the rt-PA infusion or by bolus for the initial 6 hours after infusion; a postinfusion CT scan was required before heparin treatment. The criteria for heparin use and the method of administration were at the discretion of the treating investigators. End points for analysis of safety included intracerebral parenchymal hematoma (ICH, where solid clot was clearly present and displacing brain parenchyma), hemorrhagic transformation without ICH, systemic hemorrhagic complication, and death resulting from any hemorrhagic complication. End points for potential efficacy included major neurological improvement at 2 and 24 hours and neurological deterioration. Major neurological improvement was defined retrospectively as an improvement of ≥4 points in the Stroke Scale score, with the presence or absence of major neurological improvement assessed at 2 and 24 hours after the initiation of therapy. Neurological deterioration was defined as a deterioration of ≥4 points in the Stroke Scale score at 24 hours in comparison to the baseline pretreatment.
score. The Stroke Scale was completed by the investigators, who were usually aware of previous scores for an individual patient. Patient outcome was also classified with a subjective overall assessment by the investigator (at 7–10 days and at 3 months) as completely improved, partially improved, unchanged, worsened, or dead compared with the baseline neurological status.

Posttreatment cerebral arteriography was encouraged but not required. Fibrinogens were determined using the basic clotting method of Clauss on a Baltimore Biological Laboratory Fibrinometer using Dade reagents. Fibrinogens were done in duplicate, and the average value was used. The normal range for fibrinogen is 150–400 mg/dl.

Safety and potential efficacy by dose tier were analyzed with the Mantel-Haenszel test of trend and the Mann-Whitney test.

Results

Seventy-four patients with a median age of 65.5 years (interquartile range 60–72 years) were evaluated and treated; 63 patients (85%) were white, and 11 (15%) were black; 45 (61%) were men. Prior transient ischemic attack had occurred in 13, and 13 had experienced a previous stroke >3 months before the study. Fourteen patients were taking aspirin.

Of the 74 patients treated, 71 had clinical or radiographic evidence of cerebral infarction, with the diagnosis of the remaining three consistent with transient ischemic attack. Of the 71 patients with infarction, two patients had brain stem infarctions, 40 had left cerebral hemisphere infarctions, and 29 had right cerebral hemisphere infarction; all 71 of these patients had neurological deficits at 24 hours. The infarction involved the middle cerebral artery (MCA) distribution in 61 cases (86%). After review of all clinical and radiographic results, 65 cases were thought secondary to occlusion of a large cerebral vessel (25 atheroembolic, 25 cardioembolic, 15 atherothrombotic), and six cases were thought secondary to occlusion of a small cerebral vessel. Angiographic results are reported below.
TABLE 1. Selected Methods for Urgent Evaluation and Treatment

<table>
<thead>
<tr>
<th>Method</th>
<th>Reason for exclusion</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public education through print, radio, and television media</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emphasis on pre-hospital care unit education (talks, letters, handouts)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fail-safe pager system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobile communications with transportable telephones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notification of investigators while patient en route to hospital (when possible)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multihospital network for patient entry and for education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumalike priority for in-hospital evaluation (emergency department, computed tomography, laboratory, pharmacy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent initiation of rt-PA at computed tomography suite</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

rt-PA, recombinant tissue plasminogen activator.

The mean systolic blood pressure at the time of initial physical examination at the hospital was 153 mm Hg (range 98–230 mm Hg), and the mean diastolic blood pressure was 86 mm Hg (range 50–120 mm Hg). Atrial fibrillation was present in 11 patients (15%). Maximal symptoms occurred within 5 minutes of onset in 51 (69%). The neurological examination performed just before treatment showed 24 patients with a decreased level of consciousness (32%, none in coma), 37 with forced eye deviation (50%), and 30 with hemiplegia (40%, face-arm-leg score ≥8); 16 patients (22%) had two or more of these examination findings. The median pretreatment Stroke Scale score for all patients was 12 (interquartile range 8–19).

For the 74 patients evaluated and treated, the mean time from the onset of symptoms to initiation of rt-PA was 86 minutes. Treatment began in the 90th minute for 56 patients, at 76–89 minutes for 10 patients, and within 10 minutes for eight patients. Detailed time of onset information was available for 732 excluded patients; 611 (83%) had a cerebral infarction but arrived >45 minutes after symptom onset, too late to be included in the study. Other reasons for exclusion were considerably less frequent (Table 3).

An ICH occurred within 24 hours in three of the 74 treated patients (4%) (Figure 2). The first patient was a 65-year-old man who became stuporous 2 hours and 40 minutes after cessation of an infusion of 0.95 mg/kg rt-PA given over 1 hour. The cerebellar hemorrhage was outside the region of clinical infarction and was associated with severe, sustained hypotension (nadir 59 mg/dl). His pretreatment Stroke Scale score was 5; at 3 months, he remained dysarthric and unable to walk.

Intracerebral hematoma was related significantly to time of onset from 67.7–73.0 mg/kg rt-PA given over 90 minutes. The hematoma was into the region of infarction suspected clinically. His pretreatment Stroke Scale score was 6; at 3 months, he was disabled and unable to walk secondary to his right parietal lobe deficit. The third patient was a 63-year-old woman who became drowsy and vomited 1 hour after receiving 0.95 mg/kg rt-PA over 90 minutes for dysphasia, right homonymous hemianopsia, dysarthria, right hemiparesis, and right hemisensory loss. A left thalamic hematoma was identified (Figure 2), and a left thalamic infarction was suspected but not clearly established. She died on the third day of a malignant ventricular arrhythmia associated with a preexisting cardiomyopathy and acute left ventricular failure. Her pretreatment Stroke Scale score was 22.

Intracerebral hematoma was related significantly to the total dose of rt-PA (p = 0.045, Table 2) but could not

TABLE 2. rt-PA Dose Escalation and Patient Outcome

<table>
<thead>
<tr>
<th>Dose tier</th>
<th>rt-PA dose (mg/kg)</th>
<th>No. of patients</th>
<th>Dose range (mg)</th>
<th>No. with hematoma</th>
<th>No. with other major hemorrhagic complications</th>
<th>No. with MNI at 2 hours†</th>
<th>No. with MNI at 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.35</td>
<td>6</td>
<td>22–25</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>0.60</td>
<td>12</td>
<td>10–46</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>III</td>
<td>0.85</td>
<td>10</td>
<td>45–60</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>IV</td>
<td>0.85§</td>
<td>20</td>
<td>46.4–86.6</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>IV-E</td>
<td>0.95§</td>
<td>22</td>
<td>53.9–82.5</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>V</td>
<td>0.95§</td>
<td>3</td>
<td>67.7–73.0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>VI</td>
<td>1.08§</td>
<td>1</td>
<td>81.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>74</strong></td>
<td><strong>3 (4%)</strong></td>
<td><strong>2 (3%)</strong></td>
<td><strong>2 (22%</strong></td>
<td><strong>0 (30%)</strong></td>
<td><strong>34 (46%)</strong></td>
</tr>
</tbody>
</table>

rt-PA, recombinant tissue plasminogen activator; MNI, major neurological improvement (improvement of ≥4 points in National Institutes of Health Stroke Scale score).

§Hematoma related to increasing rt-PA dose, p = 0.045 Mantel-Haenszel test, 0.03 Mann-Whitney test.
†≥4-point improvement at 2 hours not related to increasing rt-PA dose, p>0.76 Mantel-Haenszel test.
*One patient was given 46 mg in error (40-mg dose cap).
%Ten percent of the dose given as a bolus.
[Ninety-minute infusion (all other patients had a 60-minute infusion).
$Dropped back to lower dose tier because of hemorrhagic complications.

TABLE 3. Exclusions From Urgent Patient Treatment

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (arrived &gt;45 minutes after symptom onset)</td>
<td>611 (83)</td>
</tr>
<tr>
<td>On time, but one or more other exclusions*</td>
<td>121 (17)</td>
</tr>
<tr>
<td>Diagnosis other than acute stroke</td>
<td>62 (51)†</td>
</tr>
<tr>
<td>Hemorrhagic stroke by computed tomography</td>
<td>32 (26)</td>
</tr>
<tr>
<td>Sensory loss alone or ataxia alone</td>
<td>20 (16)</td>
</tr>
<tr>
<td>Patient too old</td>
<td>19 (16)</td>
</tr>
<tr>
<td>Excessive blood pressure</td>
<td>15 (12)</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>5 (4)</td>
</tr>
</tbody>
</table>

*Twenty-five percent of these 121 patients had two or more reasons for exclusion.
†Represents percentage of the 121 patients arriving on time.
FIGURE 2. Computed tomographic scans from three patients who developed symptomatic intracerebral parenchymal hematoma after recombinant tissue plasminogen activator (rt-PA) therapy. Left panel: A 65-year-old man developed a cerebellar hematoma after infusion of 0.95 mg/kg rt-PA over 1 hour in the setting of severe hypofibrinogenemia. Middle panel: A 62-year-old man with acute left hemiparesis became obtunded with vomiting and increasing weakness 1 hour after treatment with 0.95 mg/kg rt-PA given over 90 minutes, and a right parietal hematoma was detected. Right panel: A 63-year-old woman with acute right hemiparesis and hemisensory loss became drowsy and vomited 1 hour after receiving 0.95 mg/kg of rt-PA over 90 minutes, and a left thalamic hematoma was detected.

be related to any other clinical variable. For example, the three patients with ICH had blood pressure readings during the infusion that were ≥160 mm Hg systolic or 90 mm Hg diastolic, but so did 27 of the 71 without ICH; one of the three patients with ICH had been taking aspirin, but 13 of the 71 without ICH had been taking aspirin. Asymptomatic hemorrhagic change was noted by CT at 24 hours in three patients (4%) and was not dose related (Figure 3); the baseline Stroke Scale scores and dose tiers were 8, tier IV; 20, tier IV; and 22, tier IV. None of the patients with ICH received heparin, although 18 patients without ICH received full-dose intravenous heparin in the first 18–30 hours after treatment (two in the first 6 hours), and two patients received subcutaneous or mini-dose intravenous heparin in the first 18–30 hours.

Two major systemic hemorrhagic complications occurred. Subpericardial hemorrhage, with pericardial tamponade developed in a 63-year-old woman 5 days after acute myocardial infarction and 1 hour after 0.95 mg/kg rt-PA administered over 60 minutes for a left MCA distribution cerebral infarction. Two hours after the rt-PA infusion the PT was 16.5, the activated PTT was 37.5, and the fibrinogen was 86 mg/dl. A second patient, who had the onset of her stroke immediately after a transfemoral cerebral arteriogram (angiography was not an exclusion), sustained a retroperitoneal hematoma that was identified 24 hours after the cessation of a 90-minute infusion of 0.95 mg/kg rt-PA. The patient was also on intravenous heparin that was started 12 hours after rt-PA infusion had been completed. All other bleeding complications were minor and included gingival bleeding (n=6), hemoccult positive emesis (n=3), and bleeding or oozing at puncture sites (n=3).

Major neurological improvement at 2 hours (≥4-point decrease in Stroke Scale score) occurred in 22 patients (30%). The median pretreatment score for this group was 14, and the median improvement at 2 hours

FIGURE 3. Computed tomographic scans performed at 18–30 hours showed hemorrhagic change in three of 71 patients without hematoma. CT findings were asymptomatic and were not associated with neurological deterioration. Right panel: Acute infarction involves the deep right hemisphere; a well circumscribed old left hemispheric infarction is also seen.
was 8.5 points. For example, a patient with a score of 14 might have inability to speak or comprehend, complete right facial paresis, inability to resist gravity with the right arm and leg, and a dense right hemisensory impairment (Figure 1); an 8-point improvement at 2 hours might correspond to word finding difficulty, mild dysarthria, minor right facial paresis, and slight hemiparesis with only a drift of the outstretched arm or leg.

The median pretreatment score for those without major neurological improvement at 2 hours was 12, and the median change at 2 hours was zero points. The occurrence of major improvement at 2 hours was not related to the dose of rt-PA (p=0.76, Table 2), patient age, race, or gender, location of the infarction, type of infarction (see “Appendix”), or severity of the pretreatment neurological deficit.

Major neurological improvement at 24 hours (≥4 points) occurred in 34 patients (46%), and 18 of the 34 had major improvement at 2 hours (Table 2). Neurological deterioration at 24 hours (≥4-point increase in deficit) occurred in eight patients, two of whom deteriorated secondary to ICH. At 7–10 days, patients were determined to have extended their original infarction; two patients sustained the deterioration in the first 24 hours, one patient deteriorated in the first week after initially improving 9 points in the first 24 hours, and three patients deteriorated after the first 24 hours. Neurological deterioration did not relate significantly to the type of infarction, the use of heparin, or the presence of arterial occlusion by arteriography. We suspected reocclusion in one of our patients, who had dramatic neurological improvement 30 minutes into his rt-PA infusion; his arteriogram the following day showed a partially recanalized thrombus in the MCA trunk. Unfortunately, on the fourth day he became hemiplegic and developed a large MCA distribution infarction by CT scan, suggesting MCA occlusion. Another patient with cardiomyopathy and atrial fibrillation may have had fragmentation of a preexisting thrombus.12 He had a sudden MCA distribution infarction (incomplete parietal branch occlusion by arteriography), demonstrated major neurological improvement during and after rt-PA therapy, but then sustained a posterior cerebral artery distribution infarction on the fourth hospital day. His transthoracic echocardiogram was normal.

Six patients (8%) died within 30 days. One death was identified as possibly related to rt-PA therapy (Figure 2). Three patients died of cerebral edema (fourth day, eighth day, eighth day); arteriography was performed on one of the three and showed occlusion of the MCA trunk; none of these three patients were among those who worsened within the first 24 hours. Six patients died at 30 days to 3 months, and three of the deaths were clearly related to the cerebral infarction (extension of cerebral infarction following angiography, pneumonia, and status epilepticus). At 3 months, 24% of all patients were subjectively rated as completely improved, 45% as partially improved, 12% as stabilized, 3% as worse, and 16% as dead.

Patients with major neurological improvement at 2 hours developed smaller infarctions by CT than did patients without major improvement (Table 4) (p<0.01 by Student’s t test). There was no relation between infarct volume and rt-PA dose (mean infarct volume 45±68 cm³ for rt-PA doses ≤0.85 mg/kg and 46±64 cm³ for doses >0.85 mg/kg). Edema with mass effect was identified by CT in the region of the infarction in 28 of the 74 CTs performed at 18–30 hours and in 31 of the 70 CTs performed at 7–10 days. The presence or absence of edema was not related to major neurological improvement at 2 hours. Whether edema in some cases could have related to reperfusion could not be determined because arteriography was not performed before rt-PA treatment.

Cerebral arteriograms were performed after treatment in 54 patients and were completed within 24 hours of symptom onset in 25. The arteriograms were interpreted locally by investigators who were not blinded to the clinical outcomes. Forty of the 54 patients (74%) had evidence of thrombus within one or more arteries ipsilateral to the clinically impaired hemisphere. One or more complete arterial occlusions were identified in 27 patients (50%) (Table 5), with posttreatment occlusion not significantly related to the absence of major improvement at 2 hours (p<0.10).

Hypofibrinogenemia to a concentration of <100 mg/dl occurred in seven patients (9%) at 3 hours from...
the initiation of rt-PA. The relation of hypofibrinogenemia to increasing doses of rt-PA neared statistical significance \( (p=0.052) \), and six of the seven patients had a fibrinogen concentration of <50 mg/dl.

**Discussion**

Patients with acute stroke can be evaluated neurologically, studied with brain CT, and treated within 90 minutes of symptom onset. Urgent treatment was accomplished in this study at large urban teaching hospitals (600-1,500 beds) and at small community hospitals (160-245 beds). Such rapid patient identification, transport, evaluation, and treatment have not been reported previously. The time-dependent vulnerability of the brain to ischemia suggests the importance of similar urgency for future therapeutic trials.

When administered very early after symptom onset, intravenous rt-PA was relatively safe with regard to hemorrhagic complications. At doses <0.95 mg/kg, ICH did not occur, and the hemorrhagic conversions were asymptomatic (Figure 3). At doses \( \geq 0.95 \) mg/kg, ICH occurred in three of 26 patients (11%) and was identified within 3 hours from the end of rt-PA infusion for each case. Higher doses of rt-PA were thus associated with ICH \( (p=0.045) \), but the relation should be interpreted cautiously because small numbers of patients were studied at each dose, and only three cases of ICH occurred. In addition, the hematomas were heterogeneous. One occurred within presumably normal brain, and the other two occurred within the presumed region of infarction.

Comparison of the hemorrhage rate with the natural history in stroke patients is difficult because the rate of very early hematoma formation or hemorrhagic transformation in the absence of thrombolytic or anticoagulant therapy has not been firmly established. Autopsy series are not representative and cannot precisely date the onset of hemorrhagic change. In clinical reports, the second CT performed after symptom onset has usually not been required for all stroke patients by protocol, or a second CT was required but was performed beyond the first 48 hours after symptom onset. In a series of 160 consecutive patients with embolic stroke, hemorrhagic infarction or hematoma formation developed in 65 but was detected in <1-4 days in only 10 (6%). Hematoma with mass effect occurred in three of 140 patients (2%) who did not receive urokinase or heparin therapy and in four of 20 (20%) who did, with hematoma more common in the elderly. The timing of the hematomas was not reported, and CT scans were not required at 24 hours.

For stroke patients treated with rt-PA, information regarding brain hemorrhage is now becoming available. In a randomized trial of rt-PA, Mori and colleagues reported hemorrhagic transformation in 10 of 19 patients (53%) given rt-PA and in five of 12 patients (42%) given placebo. Hematoma formation, including number and timing, was not reported. In a dose-escalation trial of 104 patients treated with intravenous rt-PA within 8 hours of symptom onset, hemorrhagic infarction occurred in 23 (22%) and hematoma occurred in 10 (9.6%); neither was associated with prior aspirin use, hypertension, or rt-PA dose, but hemorrhagic infarction and hematoma were more likely in patients treated >6 hours from symptom onset. A dose effect for rt-PA and brain hemorrhage has been reported in patients without acute brain injury who were given rt-PA as therapy for acute myocardial infarction; the rate of ICH in that setting was higher when large doses of rt-PA were used (150 mg). In our patients, risk factors for rt-PA-related ICH other than dose were not identified, nor have risk factors for ICH been established in studies of other thrombolytic agents used as treatment for stroke.

Nonhemorrhagic complications of rt-PA therapy were not observed in this study. Fatal reperfusion edema has been suggested as a potential risk of thrombolytic therapy for stroke. In our series, edema with mass effect on CT developed in 28 patients at 18-30 hours. There was no difference in the evidence of edema formation between patients with and without major neurological improvement at 2 hours. Although some of the patients deteriorated in association with the observed mass effect, frequently the finding on CT was not associated with any clinical change, or it was associated with neurological improvement. Postthrombolytic reocclusion has been reported in 15-20% of patients treated for acute myocardial infarction. We suspected reocclusion in only one of our patients (see above). Thrombolytic fragmentation of a preexisting thrombus with embolization to the brain is another possible neurological complication and may have occurred in one of our patients.

Therapeutic efficacy for rt-PA cannot be inferred from this uncontrolled safety study. Nonetheless, major neurological improvement within 2 hours after initiation of rt-PA occurred in 22 of 74 patients (30%) and in 19 of 71 (27%) who were subsequently diagnosed to have sustained a cerebral infarction. Unfortunately, the rate of spontaneous improvement in the first 90-180 minutes after stroke onset is not known, and results from the placebo groups in recent therapeutic trials do not include examinations in the first 6-12 hours after symptom onset. Biller et al examined 29 consecutive patients with acute ischemic stroke within 12 hours of symptom onset and used the NIH Stroke Scale supplemented with a motor scale (expanding the highest abnormal score from 42 to 82). These patients received no specific treatment, and eight (28%) improved ≥4 points after 2 hours of observation. The median baseline score for this group was 16.5, and the median improvement was 7 points, but the degree of improvement is not directly comparable because of the expanded scale. In our study, the occurrence of major improvement could not be related to the type of cerebral infarction (e.g., cardioembolic), but the number of patients studied was too small to allow any conclusions regarding the type of stroke potentially most amenable to thrombolytic therapy.

It should be noted that the patient population for this study was not representative of the general stroke population. Ninety percent of patients had large vessel distribution infarctions, and only 3% had brain stem infarctions. Thirty-two percent of our patients had a decreased level of consciousness, 40% had hemiplegia, and 50% had forced eye deviation. We suggest that patients with a dramatic clinical deficit are more likely to be recognized as dangerously ill by family members.
and pre-hospital care professionals, resulting in more rapid transport and evaluation.

Finally, these pilot observations provide initial guidance regarding dose recommendations for use in future trials. The lack of evidence for greater neurological improvement at higher dose levels and the suggestive evidence linking higher rt-PA doses to increased risk of serious hemorrhage led to the termination of the pilot study. For future placebo-controlled studies, we recommend evaluation of an intermediate dose of 0.85–0.95 mg/kg rt-PA intravenously over 60–90 minutes, when this dose can be administered within the first hours after symptom onset. Further definition of differences in benefit and risk between this dose and other doses would require study randomizing among doses. We also recommend that patients be considered for inclusion into therapeutic trials of thrombolytic therapy regardless of suspected stroke type. Differences in hemorrhagic risk or neurological benefit of rt-PA as therapy for particular stroke types are not yet evident.

Appendix

Current Clinical Diagnosis of Stroke Type: The investigator was asked to make a retrospective assessment of the mechanisms of the entry stroke event based on all available clinical and laboratory data. The following definitions were used:

1. Large vessel atherothrombotic: Stepwise or stuttering onset of the entry neurological deficit; may have history of transient ischemic attacks. Clinically, region of brain involvement not consistent with cortical branch occlusion. Posttreatment angiogram shows large vessel occlusion without evidence of distal emboli. If entry neurological deficit persists after treatment, CT scan demonstrates infarction in watershed zones or entire territory of occluded vessel.

2. Large vessel atheroembolic: Abrupt or rapid onset of entry neurological deficit. May have history of transient ischemic attacks. Posttreatment angiogram or ultrasound shows embolic source in carotid or vertebrobasilar system. If carotid occlusion and distal branch emboli are both demonstrated, code as large vessel atheroembolic.

3. Cardioembolic: Abrupt or rapid onset of entry neurological deficit. Definite cardiac source of embolus identified, preferably with angiographic or noninvasive exclusion of large artery source.

4. Other ischemic stroke type:
   a. Lacunar infarction: Entry neurological deficit must conform to one of the classic lacunar syndromes (pure sensory stroke excluded). History of hypertension or diabetes present. No cardiac source of embolus is identified and posttreatment angiogram shows large vessel occlusion without evidence of distal emboli. If entry neurological deficit persists after treatment, CT scan demonstrates infarction in watershed zones or entire territory of occluded vessel.
   b. Embolic, unknown source: Abrupt onset of neurological deficit with angiographic documentation of embolic material seen. No identifiable source of embolus established.
   c. Mechanism uncertain, complete work-up: Despite exhaustive search, no cause for the entry deficit can be identified. Negative angiography is generally required.
   d. Mechanism uncertain, abbreviated work-up: Exact mechanism not established because, for whatever reason, a full diagnostic evaluation was not clinically appropriate or was refused by the patient.
   e. Other ischemic stroke type: Specify.

Acknowledgments

We acknowledge the assistance given by the paramedic units and by the health professionals at the 12 participating hospitals: Cincinnati/Northern Kentucky; Good Samaritan Hospital, University Hospital, The Christ Hospital, Providence Hospital, the St. Luke Hospitals, St. Elizabeth South Medical Center, Bethesda North Hospital, St. Francis/St. George Hospital; New York: New York Hospital; Virginia: University of Virginia Medical Center, Winchester Medical Center.

References

Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes.
T G Brott, E C Haley, Jr, D E Levy, W Barsan, J Broderick, G L Sheppard, J Spilker, G L Kongable, S Massey and R Reed

Stroke. 1992;23:632-640
doi: 10.1161/01.STR.23.5.632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/23/5/632

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke 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 Stroke is online at:
http://stroke.ahajournals.org//subscriptions/